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MODELLING OF MOLECULAR STRUCTURES AND PROPERTIES IN PHYSICAL CHEMISTRY AND BIOPHYSICS

FORTY-FOURTH INTERNATIONAL MEETING
QUARANTE-QUATRIÈME RÉUNION INTERNATIONALE

MODELISATION DES STRUCTURES ET PROPRIETES MOLECULAIRES EN CHIMIE PHYSIQUE ET EN BIOPHYSIQUE

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Nous exprimons à tous notre gratitude pour ce soutien.

GENERAL THEORY OF INTERMOLECULAR FORCES

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ABSTRACT

There is much current interest both in inter-and intra-molecular potential energy surfaces. The structure and properties of van der Waals molecules and clusters provide an important source of information about molecular interactions. This information can be used to generate intermolecular potentials that can be useful in descriptions of larger systems, such as condensed phases, solutions of surfactants, and biomacromolecules. It is convenient to divide intermolecular potentials into long-range and short-range components. The former are related via perturbation theory to the charge distribution and polarizabilities of the free molecules, and the resulting long-range potentials vary as an inverse power of the separation between the molecules. The short-range interactions result from the overlap of the electron clouds of the interacting molecules and diminish exponentially with the separation. By dividing the molecules into atoms or small groups of atoms, it is possible to obtain convenient and convergent representations of the potential. The approach can be used to provide a theoretical basis for the popular site-site potential models that are now used extensively in computer simulations. Attention will be paid to the additivity or non-additivity of potentials, to the rôle of the solvent in solutions, and to changes in the electronic properties, such as the dipole moment, that result from intermolecular forces.

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2

A VIBRATIONAL MOLECULAR FORCE FIELD FOR MACROMOLECULAR MODELLING

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An intramolecular force field has been developped for various building blocks with biological interest (amino-acids, peptides, nucleotides and saccharides). A UREY-BRADLEY-SHIMANOUCHI type expression has been used for the potential energy function. The corresponding parameters are obtained on the basis of vibrational frequencies through normal modes analysis for the crystals. In order to extract the best set among the various force fields able to reproduce frequencies, additional data are needed. At the present time they consist of infrared and resonance Raman intensities and temperature factors given by the X rays studies. The transferability of the final set is also checked on larger systems and then used for molecular mechanics and dynamics calculations. A harmonic dynamics study of bovine pancreatic trypsin inhibitor and a turn of the left handed Z- DNA helix will be presented and compared with previous published works.

3

MODELLING OF BIOMOLECULAR PROPERTIES BY MOLECULAR DYNAMICS SIMULATION

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During the last decade it has become feasible to simulate the dynamics of biologically relevant molecules on a computer. The method of molecular dynamics (MD) solves Newton's equations of motion for a molecular system, which results in trajectories for all atoms in the system. From these atomic trajectories a variety of properties can be calculated.

Computer simulation of molecular systems aims at *macroscopic* behaviour to be computed from *microscopic* interactions. The main contributions of the microscopic point of view are (1) understanding, (2) interpretation of experimental results, (3) semiquantitative estimates of experimental results and (4) the capability to interpolate or extrapolate experimental data into regions that are hard to reach in the laboratory.

One of the two basic problems in the field of molecular modelling and simulation is how to efficiently search the vast configuration space which is spanned by all possible molecular conformations for the global low (free) energy regions which will be populated by a molecular system in thermal equilibrium. The other basic problem is the derivation of a *sufficiently accurate interaction energy function or force field* for the molecular system of interest. It belongs to the art of computer simulation to choose the unavoidable assumptions, approximations and simplifications of the molecular model and computational procedure such that their contributions to the overall inaccuracy are of comparable size, without affecting significantly the property of interest.

Some practical applications of computer simulation in the field of (bio)chemistry will be reviewed.

4

THEORETICAL STUDY OF A CONFORMATIONAL CHANGE IN AN ENZYME : METHODOLOGY AND FIRST RESULTS ON CITRATE SYNTHASE

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Following the lines and using the codes developped in Harvard by M. Karplus and his colleagues, we introduced an alternative strategy for dynamical calculations on proteins at various time scales. It essentially consists of the following steps.

(i) We construct a set of internal vectors by the principle of the binary tree, adapted to the peculiar structure of each residue and to the secondary and tertiary structures of the protein. The transformation from Cartesian coordinates, velocities and energy gradients to the new set and vice versa needs purely topological, constant matrices ; the kinetic energy remains diagonal and thus simple Newtonian dynamics may be used.

(ii) From these internal vectors we generate a set of relative polar coordinates and determine through a dynamical test the frequencies associated with each of these coordinates, which permits a classification of slow and fast modes.

(iii) We then compared a regular dynamics by the CHARMM programs, using a 1 fs integration step, with a constrained dynamics using 10 fs steps after freezing all modes of frequencies larger than 10^{13} s^{-1}. It appears that the main features of the dynamics of the slower modes are preserved, apart from phase shifts occuring during the freezing process.

(iv) Iteration of this procedure to larger time scales is possible providing averaged forces are used for the hydrogen bonds. One may then hope to obtain significant collective modes by diagonalization of the correlation matrix of slow mode amplitudes.

5

Design and Synthesis of a new bifunctional microprotein by interactive modelling

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EETI II, a 28 residues, three disulfide bridges microprotein has been isolated from the cucurbitacaea Ecballium elaterium. It behaves as a powerful trypsin inhibitor with a dissociation constant of $10^{-12}M^{-1}$. Its chemical synthesis has been achieved that provided enough material to make a complete 2D ^1H NMR study ; then the 3D model was built using the DISGEO method, giving the tertiary structure and the disulfide bridges arrangement. The DISGEO structure was then optimized by Restrained Molecular Dynamics. A radiocrystallographic study of the EETI II/ Trypsin complex confirmed the NMR attributions. The synthesis of peptides bearing selected modifications at the reactive site has been successful. The new products show high inhibiting power towards elastase or chymotrypsin, while their affinity towards trypsin vanished. The topological analogy of EETI II to the known Carboxypeptidase A inhibitor from potato suggested to build a chimeric molecule bearing two active sites against both trypsin and carboxypeptidase A. A 32-peptide designed by interactive model building was synthetized that could be proven to bind both enzymes.

POTENTIEL MAPS OF METHANE, WATER AND METHANOL IN SILICALITE

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Silicalite is a form of pure crystalline silica that represents the end member ($Si/Al\infty$) of the high-silica ZSM-5 zeolites. It provides an example of a microporous adsorbent without any adsorption sites of chemical nature, which adsorption properties are only related to the channel structure.

The interaction energy of silicalite clusters with methane, methanol and water has been calculated and optimized with respect to the orientation for many positions inside the channels. The calculations were performed in the atom-atom approximation with parameters deduced from ab-initio studies of small systems. The electrostatic terms are evaluated by using multicentered multipole expansions, limited to charges and dipoles distributed on all the atoms. For the silicalite crystal, the whole multipole expansion was reconstructed from those of fragments, especially dimers $(HO)_3SiOSi(OH)_3$ and monomers $Si(OH)_4$, by superposition and substraction of parts in excess. Concerning the silicalite clusters, we selected a set of cylinders surrounding the different parts of the channel network. All silica tetrahedra located inside one of these cylinders were taken into account and the free valences were saturated with hydrogen atoms. The potential maps represent the distribution of the interaction energy of one adsorbed molecule, averaged over different orientations.

Approximate values of diffusion barriers are deduced from the potential maps and the initial heats of adsorption are evaluated by average over the positions and the orientations, with the hypothesis of a Boltzman distribution.

Our values are qualitatively in accordance with the experimental results. In particular the orders $CH_4 < H_2O < CH_3OH$ for the heat of adsorption and $CH_4 > H_2O > CH_3OH$ for the mobility inside the crystal are well reproduced. The values of the initial heat of adsorption (9.4 kcal/mol for CH_4, 12.5 for H_2O, 16.7 for CH_3OH) are too large by 2 kcal/mol. They are very sensitive to the experimental geometry adopted for silicalite.

7

Chemisorption on Transition Metal Surfaces and Heterogeneous Catalysis: Back-of-the-Envelope Theoretical Modeling

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The lecture will concentrate on realistic calculations of reaction energy profiles on metal surfaces, comprising heats of adsorbate chemisorption Q and activation barriers ΔE^* for adsorbate transformations. The framework is the "back-of-the-envelope" BOC-MP (bond-order conservation Morse-potential) model providing the rigorous analytic formalism to calculate the values of Q and ΔE^* for diatomic admolecules (1). This formalism can be applied to polyatomic molecules as well if their total bond energies in the gas-phase are effectively partitioned into two-center contributions. The partitioning procedure resembling the use of Pauling resonance structures will be described. As examples, the BOC-MP projections concerning CO hydrogenation, C_2 hydrocarbon transformations, and HCOOH decomposition on transition metal surfaces will be discussed in detail, in particular the preferred coordination modes of polyatomic adsorbates and the relative preference of various conceivable reaction pathways. We will demonstrate the basic consistency of the BOC-MP results with experiment, especially when they are at variance with other theoretical approaches. It appears that the BOC-MP modeling provides a practical means for understanding and projecting surface reactivity.

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8

Theoretical models for intermolecular potentials

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It is now possible to carry out accurate *ab initio* calculations on molecular complexes by a variety of techniques. The supermolecule approach is widely used, and is capable of high absolute accuracy, but it is subject to Basis Set Superposition Error, especially when electron correlation is taken into account, and this is a difficulty when accurate calculations of small interaction energies are required. Perturbation theory gives a more detailed description of the interaction than the supermolecule approach, and consequently provides more physical insight into the nature of the interaction, but it does not converge if the interaction is too strong, that is when the distance of approach is too short, although in practice the results are satisfactory to distances inside the potential minimum. Both of these methods require calculations to be carried out at a wide range of dimer geometries if a full description of the potential energy surface is needed, and this is extremely time-consuming.

A useful alternative approach is to isolate the components of the perturbation expansion, namely the repulsion, the electrostatic interaction, the induction, the dispersion and the charge transfer terms, and to calculate each of them independently by the most appropriate technique. Thus the electrostatic interaction can be calculated accurately from distributed multipole descriptions of the individual molecules, while the induction and dispersion contributions may be derived from polarizabilities of the individual molecules. This approach has the advantage that the properties of the monomers have to be calculated only once, after which the interactions may be evaluated easily and efficiently at as many dimer geometries as required. For this reason it is possible to carry out much more accurate calculations than are possible if a complete SCF calculation on the dimer has to be done at each dimer geometry.

MODELING OF ORGANOMETALLIC REACTIVITY USING A COMBINATION OF EXTENDED HUCKEL AND MOLECULAR GRAPHICS TECHNIQUES

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A new formalism has been developed in order to evaluate the intermolecular interaction energy between an organometallic or inorganic substrate S and an incoming reactant R in the framework of the extended Hückel (EH) method. Approximate procedures are used to estimate electrostatic (E_{es}), charge transfer (E_{ct}) and exchange repulsion (E_{ex}) components, which leads to short response times allowing to use the model on an interactive graphics facility. In addition to the electrostatic potential of S, evaluated using EH wavefunctions and the NDDO or the Mulliken approximations for the one-electron integrals, we are taking account of the S-R orbital interactions which allow to estimate the E_{ct} component. Finally, the the short-range E_{ex} exchange repulsion energy is approximated using the hard spheres model for S-R interaction on the molecular surface of S. The total S-R interaction energy is then used as a reactivity index and evaluated at selected points belonging to the molecular envelope of S, a proton with an empty 1s orbital being chosen as the model electrophile, and an H^- hydride ion with two 1s electrons as the model nucleophile.

Color-coded three-dimensional Connolly dot surfaces are used for the graphics representation of the reactivity index of the substrates, together with special procedures we have recently developed on the PS-390 in order to generate solid models clipped so as to allow the simultaneous visualization of the structural skeleton. On the basis of the results obtained for a large series of organometallic reactions, this model is shown to describe adequately the initial stage of electrophilic and nucleophilic addition or substitution mechanisms. In particular, ferrocene and iron pentacarbonyl are correctly predicted to undergo an electrophilic attack on metal, whereas for arene-$M(CO)_3$ species and their derivatives, the nucleophilic attack takes place as expected on the exo-face of the ligand ring. When applied to the modellization of organometallic reaction mechanisms, the combination of simple quantum chemistry methods and molecular graphics techniques seems therefore able to bring an interesting contribution towards a better understanding of the processes of specific interactions between chemical species.

10

GENMOL

A FAST PROGRAM FOR MOLECULAR MODELIZATION

APPLICATION TO THE DETERMINATION OF THE ORIGIN OF THE PSYCHOTONIC OR SEDATIVE ACTIVITY OF TRICYCLIC ANTIDEPRESSANT DRUGS.

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Conventional methods of molecular mechanics allow to achieve the molecule geometry by minimization of the total strain energy, using partial derivatives of this energy on each atom.

- Such calculations are time consuming (the number of optimization cycles increases with the number of atoms).
- The molecular geometry which is obtained to the closest energy minimum of the starting point, without any possibility to know whether this minimum is the deepest one (generally the conventional methods do not perform conformational analysis).

The aim of our program named GENMOL is above all to generate the most stable conformations of a molecule. The calculations are based on the concept of pivots which may be bonds or not. A hierarchy of the deformations is defined (torsion, bending and stretching). The program links optimized fragments of molecules coming from differents libraries. Conformational analysis is performed during the building of the molecule and the privileged conformations are kept. GENMOL is automated for polypeptides and nucleic acids (RNA or DNA).

GENMOL is one hundred times faster than equivalent programs. Bending and stretching parameters are analoguous to MM2 (ALLINGER) parameters. Torsional, van der WAALS, hydrogen bond parameters are derived from ECEPP (SCHERAGA). The electrostatic energy is computed with net atomic charges issued from DEL RE's method for the sigma part, and with an empirical approximation for the PI part in order to get PARISER and PARR values.

When the molecule conformations of 19 antidepressant tricyclic drugs are compared to those of the neurotransmitter present in the corresponding synapses, it turns out that two structurally different families exist for serotonin receptors. The psychotonic of sedative effect are related to the receptor family touched by the drug.

The calculations indicate that the serotonin receptors touched by the sedative drugs are structurally similar to histamine receptors, what means that they also affect the histaminic central nervous system and contribute to the sedative effect.

11

AN INTRODUCTION TO NUMERICAL OPTIMIZATION

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To solve an optimization problem is to find a set of variables, satisfying some given constraints, and minimizing a given cost-function. We consider only the so-called nonlinear programming problem, in which the variables vary in $\mathbb{R}^n$, and there are finitely many constraints.

The solution (if there is one) is actually approximated, using an algorithm which constructs an iterative sequence of trial solutions. The user must provide a program which, for any given value of the variables, computes the corresponding values of the cost and/or constraints (and also their partial derivatives). From this point of view, optimization is fairly similar to solution of systems of nonlinear equations.

We explain the main ideas that are used to define optimization algorithms. They are best viewed in the unconstrained case, i.e. when the variables are allowed to take any value in $\mathbb{R}^n$. In this framework, the simplest problem is when the cost-function is quadratic, say

$$f(x) = \tfrac{1}{2}x^TAx + b^Tx + c .$$

Here, A is the matrix of second derivatives of f, which actually do not depend on x. The problem then reduces to a linear system of equations: $Ax + b = 0$.

When f is not quadratic, its matrix of second derivatives varies with x. To be efficient, an optimization algorithm must somehow estimate this matrix; this gives a quadratic function, which can be used to approximate f. This is the basis for Newton-like methods, conjugate gradient, etc... We demonstrate this approach and we explain how it can be adapted in various situations, such as when the problem is large-scale, or stiff, or when it originates from a least-squares problem, etc...

Finally, we show how the above ideas can be extended to constrained situations: first in the case of linear constraints (the feasible domain is a polyhedron), and also in the general case when the constraints are nonlinear. In the former case, the sequence of iterates is usually feasible, while it can hardly be so in the latter: it is only asymptotically that nonlinear constraints are eventually satisfied.

Conformational analysis of macrocyclic receptors and of their substrate complexes. From static to dynamic models.

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Macrocyclic synthetic receptors and their complexes allow to test current theoretical and computer graphics techniques, and to provide a deeper insight into features which are essential for molecular recognition, but which may not be easily amenable to experimental studies : conformational preferences of the free and complexed receptor, effects of solvent and environment on structure, binding affinity and selectivity, macro(poly)cyclic effect, nature and orientation of the binding sites, size of the concavity, etc....

We combine molecular mechanics, molecular dynamics and Monte Carlo simulations, normal modes analysis, to adress the above questions on prototype macrocyclic compounds : crown ethers, bicyclic and tricyclic cryptands, cryptates and derivatives. From the collection of optimized structures, as well as from the dynamics studies, we get dynamic views of these systems. Their flexibility / rigidity is discussed as a function of conformation, connectivity, and topology of the free / complexed state, and the "Receptor-Substrate" complementarity.

From a technical point of view, several force field representations are compared, and the crucial role of a high quality computer graphics system to build 3D structures of "supermolecules", and to analyze static and dynamic results is emphasized.

1 3

INTERMOLECULAR FORCES IN SOME IONIC ATMOSPHERIC CLUSTERS INVOLVING WATER QUANTUM MECHANICAL AND MONTE CARLO CALCULATIONS

E. Kochanski [1], A. Rahmouni [1], R. Wiest [2]
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Quantum mechanical and Monte Carlo calculations have been performed for the atmospheric ionic clusters $H_3O^+(H_2O)_n$ and $Ca^+(H_2O)_n$, n = 1 to 9 or 10. These systems being stabilized by intermolecular interactions, special attention has been paid to a correct description of the different energetic contributions.

In a **first step**, accurate **quantum mechanical calculations** (SCF and dispersion energies) have been performed for many geometrical configurations of bimolecular systems $M^+...H_2O$ ($M^+ = H_3O^+$ and Ca^+) , allowing the **determination of parameters** in order to represent the quantum mechanical results by analytical expressions. Such expressions are used in Monte Carlo calculations, to compute the energy of any geometry of the clusters.

In most of the Monte Carlo calculations presented in this work, the energy of the clusters is represented as a sum of the interaction energies between pairs of molecules. An 'atom-atom' (12-1-6) formula , with approriate parameters, has been used to describe the interaction between the ion and one water molecule. Different fittings of the ab initio values are proposed, allowing to study the parameters effect on Monte Carlo results.

The interaction between two water molecules is taken from the work of Matsuoka et all (ref.1).

Three-body contributions are also considered, this effect being very important in some cases, in particular to describe the clustering energies of very small clusters.

Two geometries of H_3O^+ are considered : a planar and a slightly pyramidal one.

In the **second step** of the work, **Monte Carlo calculations** have been performed with the different sets of parameters determined in step 1. Energetic and structural information is then obtained and analyzed. A special attention is paid to clustering energies, which can be compared to experimental values, and to the distribution of the water molecules around the ion. The statistical distribution of the water molecules and the geometrical structure of the most stable configurations are considered .

In a **third step**, we are checking the validity of the approximations by performing ab initio calculations on some geometrical structures of special interest generated in the course of Monte Carlo calculations. **SCF calculations** are now performed on the whole clusters and not only on the bi or trimolecular systems. The nature of the filling of the first solvation shell deserves a particular attention. Let us note that we are interested in particular cases and not only in average values. Comparison with other parameters or expressions proposed in the literature will also be done.

Part of this work has already been published recently (ref. 2).

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13A

Etude comparative des interactions intermoléculaires au moyen de méthodes pertubatives et variationnelles.

Application au dimère de l'eau.

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Ce travail concerne la théorie des interactions intermoléculaires au niveau fondamental, utilisant des méthodes ab initio élaborées, aussi bien de type perturbatif que variationnel avec utilisation de bases d'orbitales atomiques de taille très importante.

Au niveau perturbatif, nous avons mis en évidence le rôle important des contributions d'échange du second ordre (d'induction et de dispersion) qui sont habituellement négligées dans les calculs d'interactions intermoléculaires. En particulier, il faut donc également tenir compte de la dispersion d'échange lorsque l'on rajoute les contributions de corrélation intermoléculaire à l'énergie d'interaction.

Cependant la comparaison avec les calculs de type variationnel montre que dans une approche purement perturbative les contributions d'ordre supérieur jouent un rôle non négligeable, même dans les régions d'équilibre du complexe.

Par ailleurs, nous présentons quelques résultats illustrant la dépendance des différentes composantes de l'énergie d'interaction avec la géométrie du dimère (différentes orientations relatives).

De nouveaux potentiels semi-empiriques calibrés à partir de cette étude sont proposés.

13 B

MODEL HAMILTONIAN AND PERIODIC HARTREE-FOCK CALCULATIONS: WATER MOLECULE IN DIFFERENT SURROUNDINGS

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ABSTRACT

Several approaches can be used to describe the water molecule in different physical and chemical environments. On the one hand is the periodic Hartree-Fock method [1] which applies to crystal phase cases such as proton-ordered ice and $LiOH.H_2O$ providing *ab initio* reference wavefunctions. On the other hand are model (or effective) hamiltonian methods in which the surrounding is represented by an effective potential. The self-consistent Madelung potential (SCMP) method [2] uses a specific form of the effective potential, involving lattice sums, adapted to ordered systems. Introduction of a general form of the atom-atom pair distribution function allows to extend this latter model to disordered situations such as pure molecular liquids. A series of calculations of the water molecule in different environments has been performed. Charge distributions (atomic multipoles and electron density maps) computed by the two methods are compared and analyzed.

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STATISTICAL MECHANICS APPROACH IN MODELING MOLECULAR STRUCTURES AND CONFORMATION-DEPENDENT PROPERTIES

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ABSTRACT

An averaged picture of the conformational possibilities of a molecule while approaching its own interactive site can be calculated through the statistical analysis of all the acceptable molecular conformations.

The CSD (Conformations Statistical Distribution) method is presented which calculates the whole rotational hypersurface of a molecule having n internal rotational degrees of freedom, through the calculation of the nonbonded intramolecular energy (Lennard-Jones term plus coulombic interaction between nonbonded atoms) for each point of a n-dimensional homogeneous grid in the surface, and then applies Boltzmann's statistical mechanics to all the allowed conformational microstates thus obtaining the statistical weights of the various minima in which the molecule can be found, the partition function, entropy and thermodynamic potentials both in the hypersurface and around the detected minima.

Some examples show the use of the calculated distribution functions in the determination of some weighted conformation-dependent molecular properties such as internal rotational freedom, molecular shape, total dipole moment and other steric and electronic features. These quantities appear suited molecular descriptors in many theoretical studies such as prediction of most probable 3-D structure in isolated molecules, structure-activity and structure-function relationships, modeling of molecular interactions with a solid surface, evaluation of intramolecular physical properties affecting packing between molecules and its modifications with temperature. In particular for representative models of flexible chain molecules the effects linked to the transformation of thermal energy absorbed by a compound into internal rotational energy can be analyzed pointing out chain conformational transitions versus temperature. These are correlated to phase transitions in the corresponding polymeric materials.

ASPECTS DE LA DYNAMIQUE DES IONS EN SOLUTION PAR SPECTROSCOPIE IR LOINTAIN

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Les spectres infrarouge lointain des halogènures alcalins LiCl, LiI, NaI, CsI et RbI en solution dans l'acétonitrile, l'acétone et le méthanol ont été enregistrés dans le domaine spectral 30-600cm^{-1}. Ces spectres présentent une forme de bande complexe caractérisée, en général, par plusieurs maxima d'absorption (ex. pour LiI/CH_3OH trois maxima à 85, 235, 460 cm^{-1}).

Une analyse théorique permet d'exprimer la densité spectrale à l'aide (i) de la fonction de corrélation du champ polarisant, émanant de la charge ionique, lorsque les ions sont dissociés, (ii) de la fonction de correlation des moments dipolaires des agrégats ioniques non dissociés et (iii) d'une fonction de relaxation structurale caractérisant le réarrangement des molécules de solvant autour de l'ion. La fonction de corrélation du champ polarisant est ensuite réduite à une expression plus manipulable en postulant que le mouvement relatif des ions par rapport aux molécules de solvant est caractérisé, aux temps courts, par une oscillation dans la cage des premiers voisins et aux temps longs, par un mouvement de diffusion translationnel. L'application de la théorie de Zwanzig-Mori à la fonction de corrélation du champ polarisant ainsi qu'à celle des ions non dissociés permet de rendre compte quantitativement des spectres IRL des ions en solution. En particulier, en utilisant le concept de potentiel de force moyenne, il est possible d'attribuer aux maxima d'absorption les fréquences de vibration des anions et des cations dans leur cage respective, d'une part, et celles des paires d'ions en contact ou séparés par une molécule de solvant, d'autre part. Ce dernier mécanisme est décrit comme le résultat d'un échange lent entre deux états énergétiques séparés par une barrière de potentiel de quelques kT

Determination of nucleic acid conformations by vibrational spectroscopy accompanied with harmonic dynamics calculations

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It is now well known that the vibrational spectroscopy can be considered as a powerful probe to identify the secondary structure of oligo- and polynucleotides. In addition of the experimental spectra interpretation, the normal coordinate analysis allows us to give a quantitative evaluation of nucleic acid structural parameters.

In our previous studies, we have carried out a systematic investigation on DNA vibration modes (1). The Wilson's GF method has been applied on the dynamic models constituted by nucleosidic residues. In this approach, a non-redundant valence force field has been employed. Recently, these calculations have been extended in order to study the 2'-deoxyribose modes as a function of the pucker pseudorotational parameters (2).

By the use of this reliable force field through the Higgs method (infinite polymeric helical chain phonon dispersion curves), we have also performed a critical discussion on the conformations adopted by poly (dG). poly (dC) in solution at various salt concentration (3).

The present work is concerned with the quantitative evaluation of the sugar conformation (P angle), as well as the purine base orientation (χ angle). The discussion will be carried out on the manner how the (P, χ) couple of structural parameters can be determined in both α and ß deoxynucleosides by the use of the vibrational markers.

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FORCE FIELD CALCULATIONS OF SIDEROPHORES. STABILITY AND CONFORMATIONS OF Fe^{III} CHELATES WITH NOVEL IRON RELATED PARAMETERS.

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Iron is essential in human where an excess is toxic, and in plants where a lack of the element causes ferric chlorosis.

Iron carriers (siderophores) are appropriate organic ligands able to complex and transport Fe^{III} for establishing an appropriate concentration level of the element. We have therefore undertaken the design and synthesis of new efficient iron chelatants.

The new ligands contain carboxy and catechol substructures arranged in order that six oxygen atoms are located at the top of an octahedral structure. The use of a "molecular model" approach, for the choice of the organic framework of the ligand, being an oversimplification, we have made a detailed force field calculation analysis with the Molecular Mechanics program **BLEMO** using the 1985 parametrization of the **ALLINGER MM2**. These calculations have needed the design and testing of new parameters, not yet available, for describing the interactions with iron.

The study of the iron complexes as a function of the ligand size and of the nature of the possible isomers shows what are the most stable structures, and helps in tailoring other ligands. The syntheses of these new siderophores are in the course.

Handling the structural information arising from molecular modeling for drug activity predictions : the SARAH system.

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The computer is a versatile tool. In particular it can perform either numerical computations or logical operations leading to a branch of Artificial Intelligence. In the case of molecules like drugs acting in complex processes, both of these capabilities may be used to set up a computer assisted drug design system. The molecular properties : geometry, conformational energies and also electronic properties can be computed by means of molecular mechanics and quantum chemistry, but handling this very rich information efficiently requires special procedures which may mimick the chemist's reasoning with the advantages of getting rid of subjectivity and performing systematic and lenghthy comparisons without the risks of human fatigue.

The SARAH system (Structure-Activity Relationships by Apprenticeship and Heuristics) rests upon the *Key-Lock* model : the substrate has to fit the receptor's site, in particular through a special molecular pattern and a shape adapted to the receptor's geometry. It also has to exhibit the proper electronic properties to make the substrate-receptor complex as active as possible.

The procedure is decomposed into three steps :

1. A characteristic pattern of heteroatoms is defined by superimposition of the active molecular skeletons to evidence the recurrent atoms.
2. Rules of activity are determined by systematically checking the correlations between the variations of shape or electronic properties around the characteristic pattern and the variations of activity relative to a reference molecule.
3. A multivariate statistical analysis is performed on the electronic properties of active molecules to extract a quantitative criterion for the activity of a new molecule.

The system is evolutive : when a new molecule has been tested, it can enter the training set and refined criteria are produced.

The possibilities of the system are illustrated by the analysis of the antiepileptic properties of a series of benzodiazepines.

RELATION ENTRE CONSTANTES DE FORCE ET CONSTANTES ELASTIQUES DANS DIVERS MATERIAUX

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Le but de ce travail est de relier l'élasticité microscopique (celle des liaisons) et l'élasticité macroscopique. Une méthode de calcul matriciel des éléments C_{ij} du tenseur d'élasticité à partir des constantes de force a été développée par Shimanouchi en 1971, reposant sur la relation générale de Born et Huang.

Nous avons écrit un programme de calcul, à partir de cette théorie, permettant de calculer les éléments C_{ij} à partir du champ de force d'un cristal. Ce calcul donne également les dérivées partielles des constantes élastiques par rapport aux constantes de force, c'est-à-dire la contribution de chaque type de liaison et de chaque type d'angle dans la valeur de la constante élastique.

Nous avons étudié des matériaux très divers dont les constantes élastiques sont connues et les résultats ont montré que :

1°) les champs de valence utilisés sont tout à fait valables pour calculer avec une bonne approximation les constantes élastiques et les fréquences de vibration.

2°) la contribution relative de chaque liaison et angle permet de mettre en évidence les paramètres qui influencent le plus le comportement élastique des matériaux :

a) les résultats obtenus pour le diamant, le graphite et le polyéthylène, montrent que les C_{ij} sont très sensibles à la dimensionalité du réseau covalent.

b) les résultats comparés du quartz alpha et de l'alumine alpha montrent l'influence de la coordinence des atomes.

c) les résultats obtenus pour $BaTiO_3$ montrent l'influence de l'orientation des liaisons par rapport aux axes du cristal. Lorsque les liaisons sont parallèles aux axes du cristal, les constantes élastiques dépendent pratiquement exclusivement de celles-ci, du moins en ce qui concerne la compressibilité.

SIMULATION OF FREE ENERGY RELATIONSHIPS FOR THE ELECTRON TRANSFER REACTION BETWEEN Fe^{-} and Fe^{2-}.

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The classical treatment of electron transfer reactions generally use an activated-complex formalism. According to the Franck-Condon principle, the electron transfer must occur at the intersection region of the diabatic potential energy hypersurfaces. This region is reached by a suitable fluctuation in the nuclear configurations of the precursor complex.

The expression of the rate constant given by the standard transition-state theory shows that it depends on the exponential factor $\exp(-\Delta g^{\neq}\beta)$ which measures the probability that the system will be in the transition-state region relative to the probability of being at the reactants region. The evaluation of the reaction rate would require an extremely long simulation time if one started at the reactans region.

In this work we present the results obtained for the electron transfer reaction between Fe^{-} and Fe^{2-}, the distance between both ions being kept fixed. Given that the two reactants are monoatomic ions, the nuclear coordinates of this system only correspond to solvent coordinates. For a sample containing 50 water molecules we have generated one million of configurations starting from the reactants region, but none of them has been found at the transition state region.

To evaluate the free energy difference we have used two different techniques. In one of them we have assumed a parabolic behavior of the free energy surface with respect to the solvent reaction coordinate. This has permitted to obtain the probability of finding configurations at the transition-state region from the calculation of several values of the logarithm of the probability corresponding to configurations lying in the reactants region. The second technique has allowed to obtain a more quantitative value using a free-energy perturbation technique with a suitable mapping potential.

POLYMORPHISM AND MOLECULAR DISPLACEMENTS IN ORGANIC SOLID STATE.

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Organic molecules often display several crystalline varieties. The relative stability of such arrangements and their mutual transformation have been the object of numerous static and dynamic models. Almost all studies are based on atom-atom potential methods. Lattice and molecular dynamic methods have been applied to plastic phase and to the corresponding ordered-disordered transition of small molecules or rigid molecules, such as benzene or naphthalene. Relative stability calculations have been often carried out for testing the efficiencies of atom-atom potential methods. Differencies, often of the order of few Kcal/mole, are generally well reproduced, even if absolute values depend of the choice of parameters.

Concerning the transition between phases, it is to be said that experimental studies show a great variety of parameter dependancy, feeding controversies. Single crystal-single crystal second order transformations sometimes are claimed to not exist. Nevertheless, such transformations would be of interest from both theoretical and experimental physic point of view, since they are conceived as cooperative displacements of molecules.

Studies of relative stabilities and mutual transformaations of phases are of special interest for pharmaceutical and industries of explosives. Polymorphism is a very usefull support for modelizing molecular motion in space. Modelization of phase transition of para-dichloro benzene and diacetamide were investigated in our laboratory and the entire transition path will serve as typical examples.

NONARCHIMEDEAN MODELING FOR BIOSYSTEMS EVOLVING ON MANY TIME SCALES

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The nonarchimedean (n.a.) analysis was used to describe relaxation processes in drug-membrane interactions, self-excitation of interfaces, the balance of entropy in biosystems which exhibit more than one time scale in their evolution [1-5]. The method relies upon the replacement of the real time t and of the evolution variable y(t) by elements of an n.a. field [1,6,7]

$T = t + \varepsilon t + \ldots + \varepsilon^M t$ and $Y(T) = y_0(t) + \varepsilon y_1(t) + \ldots + \varepsilon^M y_M(t)$

respectively, where ε is an expansion parameter and $y_m(t)$ are the components of Y(T) corresponding to the M+1 time scales. The model eqs. are then replaced by their n.a. correspondents to the result of an enriched mathematical structure of the evolution variable. Particularly, it is shown that the formalism can easily accommodate nonexponential relaxations in multi-compartmental systems (e.g. the action potential of frog sciatic nerve in the presence of anesthetics [2], cross-linking aldehydes [3]) and various regimes of chemically driven interfacial turbulence in the presence of unspecific drugs [4]. This new procedure applied to the problem of time variation of the enthropy production leads to a hierarchy of enthropy balances and of stability criteria, which can be useful in describing embryogenesis, nerve excitation and other cooperative and far from equilibrium phenomena. The existence of more than one time scale checked by the n.a. analysis suggests that the excitation or inhibition of some scale of time could be eventually used for controlling the whole process.

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CLASSIFICATION DE MOLECULES CHIMIQUES : PRESENTATION D'UNE MAQUETTE D'UN SYSTEME EXPERT

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Dans le cadre d'une initiation aux méthodes d'élaboration d'un système expert, nous présentons un programme permettant de classifier des inhibiteurs de la photosynthèse (photosystème II). Les inhibiteurs sont introduits par une description simplifiée de leur structure moléculaire (présence de certains groupes chimiques et substituants, positions relatives de ceux-ci). Des compléments de description peuvent, si besoin, être demandés par le système. Il en est déduit une prédiction de l'activité inhibitrice à partir de règles concernant des informations essentiellement topologiques. Le système peut également fournir des renseignements complémentaires détenus par la base de connaissances (bibliographie par exemple).

Le générateur de système expert utilisé dans ce travail est l'outil SPIRAL développé au CEA (Mathématiques Appliquées) par Y. SOUCHET. C'est un langage déclaratif inspiré de PROLOG avec le formalisme de la logique du premier ordre. Un formalisme objet y a été introduit: on peut y définir des classes (prototypes) et des instances de classes (objets) pour modéliser le monde étudié qui est manipulé par les règles d'inférence. La version pour micro-ordinateurs compatibles PC a été surtout employée. Des appels à des fonctions externes ont été utilisés pour la gestion de l'écran et l'affichage de textes.

SYSTEME OCTANG : UN DESCRIPTEUR 3D POLYVALENT

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La reconnaissance en 3D de fragments structuraux réels ou standard, ou de formes électroniques (Orbitales Moléculaires Potentiel Eléctrostatique...) est à la base de nombreuses stratégies de simulation moléculaire : interrogation structurale, simulation spectrale, recherche de pharmacophore et Drug Design.

Nous étudions actuellement un système de description des structures moléculaires qui repose sur une spécification qualitative des positions relatives des atomes. Ainsi plutôt que de comparer les coordonnées cartésiennes de deux points A et B, on précise que B est par exemple situé au dessus et à droite de A. Pour cela, nous utilisons les concepts d'octant et de graphe chimique : on value un arc i-j non plus par la distance interatomique mais par le numéro de l'octant localisé sur i et contenant j. Associé à une description en chemins des graphes chimiques, ce système dit "OCTANG" fournit un descripteur de forme 3D qui optimise les manipulations informatiques et permet la reconnaissance structurale sur de véritables critères de géométrie tridimentionnelle.

Le système "OCTANG" est actuellement implémenté dans le cadre du Drug Design. Toutefois cette approche novatrice, fondée sur une perception de l'environnement local des atomes doit offrir des resssources importantes dans le traitement de tous les problèmes relevant de l'identification et de la gestion de l'information structurale tridimensionnelle.

DESIGN OF NEW EFFICIENT RADICAL CLOCKS WITH THE HELP OF MOLECULAR MECHANICS

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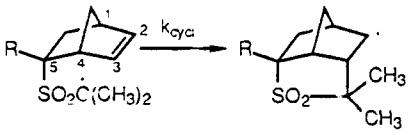
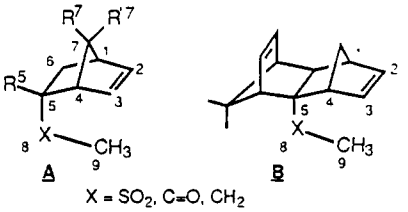
"Radical clocks[1]" names molecules able to trap by intramolecular cyclization a radical generated in an adequate position. We have synthesized these last years[2] 2-norbornenes which are very efficient α-sulfonyl radical traps, i.e. with high rates of intramolecular addition of the radical on the double bond (k_{cycl}= $2.10^8 s^{-1}$ and $10^9 s^{-1}$ at 80°C for **1** and **2** respectively). X-ray analysis has shown that the 5-*(exo)*-phenyl substituent decreases the C_4C_5S angle and consequently the minimal distance available between the reactive sites (2.50Å (C_6H_5)vs 2.70Å(CN)). It seems that the rate of cyclization is correlated to this minimal distance.



1 : R = CN
2 : R = C_6H_5



A **B**

X = SO_2, C=O, CH_2

R^5 = H, Et

R^7 = R'^7 = H, Me, iPr, -$(CH_2)_n$- n:2,4,5

In order to design new radical clocks with greatest efficiency, we performed molecular mechanic calculations on a series of molecules related to the norbornene one (**A** , **B** and few others) and studied the influence of the substitution on the distance between the reactive sites. We used the program BLEMO in the version including the MM2 parametrisation[3]. Calculations were not performed on the radicals but on the parent compounds and the minimum distance (d_{3-9}) was evaluated, after minimization ot the energy, by locking the C_3, C_5, X_8 and C_9 atoms in the same plane.

Data show the importance of the values of the $C_3C_4C_5$ and $C_4C_5X_8$ angles on d_{3-9} : a weak tightening leads to an important decrease of the distance. For this purpose, substitution on C_5 and C_7 (**A**) and dimethanonaphtalene (**B**) are the most efficient. This kind of study involving a high precision about the calculated structures is perfectly ensured by the molecular mechanics.

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Reconnaisance tridimensionnelle de pharmacophores. Application de la méthode à la comparaison morphine-enképhaline.

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Par le biais d'une technique informatique, une méthode de reconnaissance tridimensionnelle a été développée et appliquée à des composés de même activité pour lesquels la topologie du récepteur n'a pas été élucidée.

Essentiellement basée sur des critères géométriques, la méthode utilise une nouvelle définition de la molécule et de ses groupements fonctionnels afin de prendre en compte les possibles interactions avec le récepteur. Deux types de centres d'interaction (centres actifs) permettent de coder chaque molécule :

- les atomes eux-mêmes qui sont utilisés dans la plupart des comparaisons.
- les centres actifs complémentaires localisés sur le récepteur (paire électronique d'un hétéroatome, centre et direction d'un phényle).

En considérant une molécule rigide et son analogue flexible actif, le principe de la méthode consiste à comparer deux ensembles de centres actifs, un ensemble étant fixé (molécule rigide), l'autre étant renouvelé pour chaque conformation de l'analogue flexible. Afin d'éliminer le problème de l'origine des coordonnées, le produit d'autoconvolution permet de transformer deux centres actifs A et B d'origine O en un vecteur AB caractérisé par une norme et une direction. D'une façon générale, à un ensemble de N centres actifs est associé une liste de N.(N-1)/2 vecteurs, renouvelée pour chaque nouvelle conformation de l'analogue flexible. Les différents vecteurs sont alors testés deux à deux au niveau de leur produit scalaire (distance entre centres actifs) et de leur produit vectoriel (orientation des centres actifs dans l'espace).

L'introduction d'un critère énergétique basé sur les interactions entre atomes non liés ainsi que le balayage de l'espace par la technique des nombres magiques (dérivée des méthodes directes en cristallographie) permettent de réduire considérablement le nombre de solutions proposées par le programme. L'originalité du logiciel PPSP3 réside dans le fait qu'il autorise la superposition d'un nombre illimité de centres actifs.

L'application de la méthode à la comparaison morphine - Leu enképhaline fait clairement ressortir deux hypothèses de pharmacophores. L'analyse conformationnelle du pentapeptide, basée sur des critères énergétiques et les corrélations avec sa structure cristalline (Pr. Marot, Nancy, 1988) permettent de comparer les deux solutions. Les valeurs obtenues indiquent ainsi que la superposition généralement adoptée lors des relations structure-activité de ces deux composés est très peu probable. A partir de ces résultats, les principes établis du mode d'action des enképhalines au niveau du récepteur morphinique pourraient se trouver considérablement modifiés.

Conformation de molécules dans les membranes: RMN d'enképhalines et du cycloarténol

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Nous présentons deux applications de la RMN à l'étude conformationelle de molécules interagissant avec des bicouches lipidiques.

Le **cycloarténol** est un précurseur biosynthétique des phytostérols. De nombreux résultats *in vitro* et *in vivo* montrent que ce stérol a des propriétés membranaires indentiques à celles du cholestérol: c'est un bon renforçateur membranaire, contrairement au lanostérol. En vue d'expliquer ces résultats il convient de déterminer les conformations de ces composés dans les membranes. Alors que le cholestérol a un squelette tétracyclique rigide, nous avons démontré par RMN et mécanique moléculaire que le cycloarténol est une molécule flexible au niveau du cycle C. Après attribution complète des spectres ^{1}H et ^{13}C, des expériences de COSY phasée à deux températures ont montré l'existence d'un équilibre conformationel en solution [(1)]. Les résultats de RMN, en accord avec la modélisation, montrent que la conformation déterminée à l'état solide (cristallographie) n'est pas la seule existante.

Les **enképhalines** sont de petits neuropeptides hydrosolubles en échange rapide avec les membranes, pour lesquels la technique du NOE transféré en présence de lipides perdeutériés a été appliquée avec succès. Nous avons déterminé les conformations membranaires de trois analogues actifs et celle de un analogue inactif d'enképhalines (Tyr-LAla-Gly-Phe-Leu).

Les trois analogues actifs ont la même conformation membranaire constituée d'un β-turn de type II' autour des quatre derniers résidus. L'analogue inactif a une conformation différente elle aussi entièrement caractérisée et qui permet de comprendre son inactivité. Ceci met en evidence une corrélation entre activité et conformation membranaire. Ces résultats sont confrontés aux résultats obtenus par dynamique moléculaire et par mécanique moléculaire (logiciel SYBYL, TRIPOS ass.).

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25 B

Etude théorique de la structure du complexe Glutathion - Eau oxygénée

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Le glutathion, en tant que réducteur intracellulaire, joue un rôle important de protection de la cellule contre différents agents toxiques tels que certains radicaux libres, des oxygènes réactifs (en particulier ceux des peroxydes et plus précisément du peroxyde d'hydrogène) et des composés d'origine endogène ou exogène. Il est connu que la réaction d'oxydation du glutathion par l'eau oxygénée est catalysée, in vivo, par une enzyme, la glutathion peroxydase. Il a été montré récemment (A.Abedinzadeh et al. Can. J. Chem. (1989) sous presse) que même en l'absence d'enzyme le glutathion réagit rapidement avec l'eau oxygénée pour donner un complexe peroxydé. La stabilité d'un tel complexe est liée à la formation de liaisons hydrogène entre le glutathion et l'eau oxygénée (hypothèses émises par les auteurs précédents).

Nous avons donc entrepris une étude théorique sur la structure de ce complexe peroxydé, à l'état isolé ou en présence de molécules d'eau, après avoir effectué une analyse conformationnelle du glutathion dans ses différentes formes, neutre et ioniques. Les calculs ont été faits par la méthode SIBFA qui permet d'obtenir simultanément les variations d'énergies intra et intermoléculaires à partir de formules semi-empiriques ajustées sur des calculs ab initio.

25C

Etude Théorique du Transfert de Proton Intramoléculaire dans la Glycine

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Dynamique des Interactions Moléculaires

Université Pierre et Marie Curie

Nous présentons dans ce travail les premiers résultats de calculs ab initio du chemin de transfert de proton intramoléculaire dans la glycine entre ses deux formes neutre, NH_2CH_2COOH, et zwitterionique, $NH_3^+CH_2COO^-$, aussi bien pour la molécule isolée que pour la molécule solvatée par plusieurs molécules d'eau. Dans le cas de la molécule isolée, le calcul ab initio, au niveau 6-31G*, montre que la forme neutre est plus stable que la forme zwitterionique (de l'ordre de 25 Kcal/mol), et que les minima qui leur correspondent sur la surface de transfert sont séparés par une très faible barrière (point d'inflexion).

Nos calculs dans la même base montrent que lors de l'hydratation par deux molécules d'eau, la forme neutre est toujours la plus stable mais que l'écart énergetique entre les deux formes diminue, et passe de 25 à 15 Kcal/mol .

L'influence de la base a été également examinée, et notamment l'effet de fonctions diffuses et de polarisation sur la stabilité des deux formes neutre et zwitterionique de la molécule, cette dernière s'étant révélée très sensible au type de la base utilisée.

ENVIRONMENT EFFECT ON THE DOUBLE PROTON TRANSFER IN CARBOXYLIC ACID DIMERS

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The proton movement along preexisting hydrogen bonds is one of the simplest reactions. The double proton transfer (DPT) within the submolecular interpretation is assumed to be responsible for some biological processes, however, the most conclusive results are still available for simple model systems.

Quantum chemical studies of tautomeric equilibria in isolated carboxylic acid dimers point out on apparent discrepancy between theory and experiment. In the case of benzoic acid dimer the calculated activation energy for DPT was estimated to be 5 kcal/mole (or more) [1] whereas its experimental value was found to be of the order of 1-2 kcal/mole [2-3].

In this situation some reasons of the above-mentioned divergence must be taken into account. One of them is the crystal field in the solid state which in the ordered lattice reduces the barrier height by ca. 15 % [4]. According to our earlier quantum chemical calculations [5], it is concluded that the optimal field for the proton rearrangement may be realized in unordered crystal phases. The optimal tautomeric forms for the molecules around the central dimer have been predicted by expressing the environmental effects in terms of intermolecular interactions within the electrostatic approximation [6].

Some other sources of the observed discrepancy between experiment and relevant quantum chemical calculations for the proton transfer are discussed herein [5,7-8].

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EFFETS STRUCTURELS ET DE CHARGE SUR LE PHTHALOCYANINE DIMERE

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L'agrégation est un phénomène bien connu dans la chimie de la phthalocyanine. Des interactions peuvent avoir lieu entre anneaux de phthalocyanine adjacents autant en phase organique comme aqueuse. Ces associations résultent en l'accouplement de deux, ou plus, unités de phthalocyanine.

Un étude théorique de l'interaction intermoléculaire entre deux molécules de phthalocyanine a été réalisé en emploiyant un potentiel de paires atome-atome proposé par S. Fraga [S. Fraga, J. Comput. Chem., 3 (1982) 329; S. Fraga, Comput. Phys. Commun. 29 (1983) 351]. Plusieurs géométries de preuve sont optimisées avec un méthode de métrique variable.

Quelques calculs préliminaires montrent une structure face-à-face comme la conformation la plus stable pour le dimère. Dans cet arrangement, une molécule peut être tournée dans le plan par rapport à l'autre.

C'est bien connu que, en phase solide, une petite déviation des positions moléculaires relatives dans l'arrangement du cristal cause les plus grandes conséquences sur les propriétés physiques du cristal. Par conséquent, nous avons étudié l'importance de quelques paramètres géométriques (distance interplanaire, translation horizontale des anneaux, ...) de même que l'état d'oxydation de toutes les deux molécules sur l'orientation relative des molécules individuelles dans le dimère.

Aussi, on étudie d'autres aspects du dimère. L'interaction entre deux molécules apolaires vient déterminée, fondamentalment, par les moments quadrupolaires. On compare plusieurs méthodes numériques pour le calcul des moments quadrupolaires. L'effect de ces moments sur la géométrie du dimère est discuté.

Quelques conclusions préliminaires sont: 1) On recommande l'usage de charges nettes "ab initio" pour éviter problèmes de transféribilitée des paramètres d'interaction. 2) On recommande la renormalization des charges nettes pour reproduire bons moments quadrupolaires. 3) L'interpolation de polarizabilitées atomiques résulte un procédé approprié doncs les charges nettes sont modifiées.

The Na^+ ion solvation in water-hexamethylphosphoric triamide solution: MD simulation.

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The MD simulation technique has been applied to study the solvation of the Na^+ ion in binary solvent water-hexamethylphosphoric triamide (HMPT). Calculations were carried out on a periodic cubic box containing one ion, one HMPT and 205 rigid SPC water molecules. Program package MDVS designed by authors was used for simulation.
Five 5-ps MD runs in NVT-ensemble with different initial positions of the ion were performed. Both time-averaged and time-dependent properties of water molecules were calculated in the regions of the MD box, related to the polar and non-polar sites of HMPT, and in the first, second and third solvation shells of the ion separately.
Various radial and orientational distributions, velocity auto- and cross-correlation functions, structure of hydrogen-bonded network, and thermodynamic properties of the simulated system were studied. Specific results of mutual influence of sodium and HMPT on water structure and the way of ionic diffusion in solution were observed.

28 A

Monte Carlo simulation of the Acetate-Guanidinium ion pair in water

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Monte Carlo simulations have been carried out on the guanidinium/acetate ion pair in water at 25°C and 1 atm. The free energy profile of the separation of the two ions has been calculated using the statistical perturbation theory. The determined potential of mean force between the two ions set in the configuration giving the best interactions (double-bound C_{2v} configuration) shows three minima. There is no clear preference for the intimate pair (C ... C = 3.3Å) The intermediate state (C ... C = 6.3Å) is a result of cooperative binding between the ions and two water molecules forming a double hydrogen-bond bridge. The two extreme states (C ... C =3 .3Å and 9.6Å respectively) are separated by a large energetical barrier. The computed results provide insights in the effects of the solvent on an important biochemical system and anchoring site of proteins.

HIGH TEMPERATURE ANNEALED MOLECULAR DYNAMICS SIMULATIONS AS A TOOL FOR CONFORMATIONAL SAMPLING: A TEST CASE ON THE 222 BICYCLIC CRYPTAND.

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ABSTRACT:

We have performed methodological studies using "High Temperature Annealed Molecular Dynamics Simulations" (HTAMDS) on a bicyclic cryptand, with the following protocol : 100 ps of molecular dynamics at 1000°K, followed by optimisation of the structures saved every 0.2 ps, relaxation of these structures during 20 ps of molecular dynamics at 300°K and, finally, optimisation. Four sets of 500 low energy conformers of the free 222 cryptand have been produced starting either from the free cryptand or from the M^+/222 cryptate with different representation of M^+.

The analysis of these four sets allows assessment of the ability of this HTAMDS technique : (i) to interconvert experimentally known conformers starting from one of them, (ii) to locate the energy minima, (iii) to generate new conformers of low energy, and (iv) to account for the average structure observed on the NMR time scale. In view of the ionophoric behavior of the cryptand, structures are analyzed in terms of the "in/out" orientation of the binding sites.

It is found that the annealed simulations on the free molecule, although sampling largely the conformational space, do not give structures adequate for cation inclusion; however they generate the lowest energy structure known experimentally and other new closely related ones. Inclusion of cation in the simulation (either as a purely electrostatic "driver", or as a charged sphere) leads to conformations found in several complexes.

KINETIC MODELLING OF HETEROGENEOUS-CATALYZED REACTIONS WITH THE ANACIN SOFTWARE. APPLICATION TO THE HYDRODENITROGENATION OF PHENANTHRIDINE.

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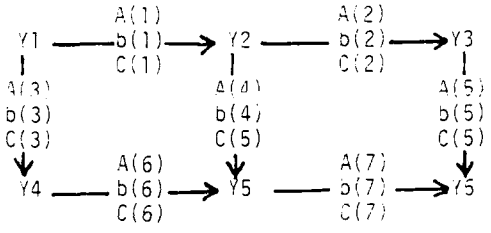
The hydrodenitrogenation of heavy hydrocarbons is represented on a laboratory scale by a simple test consisting of the conversion of alkylanilines in the presence of nitrogenated polyaromatic compounds like quinoline or phenanthridine. These compounds have been shown to inhibit the conversion of alkylanilines as due to their important concentration in the feed or to the slow progress in their own conversion. It is quite obvious that the inhibition results from competitive adsorption phenomena between the substituted anilines and the heavier N-compounds present in the feed.

In order to gain a better knowledge on the inhibiting effects and their possible quantification, a computer tool was required allowing to interpret the experimental results and to model these inhibiting effects.

A preprogrammed kinetic model consisting of six reactants, intermediates or reaction products Y1,Y2...Y6 was defined :



in which A(i) are the rate constants for the forward reactions, C(i) are those for the reverse reactions and b(i) are the constants of adsorption for the different compounds (i).

The reactions are assumed to be first order in each compound (i). The system of differential equations is integrated numerically by the Runge-Kutta method. The constants A(i), C(i) and b(i) are optimized with the simplex method to fit in with the experimental data.

In the case of the hydrodenitrogenation of phenanthridine, the residue obtained after optimization of the forward rate constants only, is relatively high ; this residue becomes smaller after optimization of both forward and reverse rate constants. Finally, the smallest residue is obtained when the optimization also takes into account the adsorption constants of the different compounds (i).

Thus, the appropriate software allows to model the inhibiting effects of nitrogenated polyaromatic compounds on the conversion of substituted anilines. This software works at a reduced running cost and requires only widely used computer equipment. It allows to determine automatically twenty constants from one set of experimental data and to visualize the results by comparing experimental and simulated curves.

28 D

Le calcul de la correction Epstein-Nesbet au second ordre de la densité électronique en tant qu'application répartie dans le contexte d'un réseau informatique local (*"Network Computing"*).

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Le Réseau Informatique Local de la Physico-Chimie Moléculaire de l'Université Pierre et Marie Curie (Paris 6) constitue un espace privilégié pour le développement d'applications réparties en Physico-Chimie Quantique. Il est présenté un tel développement pour le calcul de la correction Epstein-Nesbet au second ordre de la densité électronique dans le cadre suivant :

- développement du type Rayleigh-Schrödinger ;
- partition du type Epstein-Nesbet ;
- correction limitée au 2ème ordre ;
- référence mono-déterminantale à couches complètes ;
- a) répartition sur une station de travail multi modules de traitement ;
  b) répartition sur plusieurs stations de travail.

Les avantages (en particulier sur le plan du rapport performances/prix) et les limites d'une telle approche, par rapport à l'utilisation plus classique de "mainframes" mono ou multi-processeurs, sont discutés.

28 E

Molecular graphics for the Macintosh.

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Now that Apple Macintosh and high resolution laser printers are widely available it appears interesting to have an easy access to specifically tailored packages allowing creation and manipulation of chemical drawings for direct printing or for insertion into word processors, desktop publishers, presentation managers or graphics software.

MolDraw and MolView programs allow the production of a wide variety of display modes for 3-D molecules (Ball and stick, Space filling, Dreiding and stereo pairs of all of these). These 3-D molecules are obtained from ASCII files containing Cartesian coordinates, fractional coordinates or internal coordinates.

MolDraw and MolView programs read texfiles of atomic coordinates according to several formats, SYBYL PDB and a private format for Cartesian, fractional or internal coordinates. These text files are transfered from host computer or created on the Macintosh.

Cristallographic files include cell constants, fractional coordinates, symmetry operators and duplicate operators to display several contiguous cells.

Several parameters, such as covalent radii, atomic radii, patterns and gray tones are adjustable. Using a Macintosh II and a color monitor all models are displayed in color.

X, Y and Z rotations, translations, inversions, scaling, rotations around a non-ring bond are provided. An axis defined by to atoms can be moved to X, Y or Z axis. A plane defined by three atoms can be moved to XY, YZ or ZX plane. A cristallographic molecule may be projected onto a "hkl" plane.

Information about interatomic distances, angles or torsions are available by selecting pertinent atoms.

Several techniques have been tested for displaying depth relationships : depth-cueing, stereopsis and animation.

Stereo views are projected in either a relaxed mode, a mirror mode (one view is seen after reflexion on a mirror) or a crossed mode. The stereo separation and the rotation between stereo views are adjustable.

Animation is a very effective technique for displaying depth relationships. Successive views of a 3-D model, projected after rotation around any axis, are stored in memory and later transferred to the screen. While it is impossible to infer the sense of rotation from orthonormal projections of wire-frame models, using depth-cueing, ball and stick or space filling models, the sense of rotation can be easily deduced. The number of animated images and the animation speed depend on the size of the front window and on the size of available memory.

Most models are generated in less than 3 seconds on screen. A black and white shaded space-filling image of a 500 atoms molecule was generated in 30 seconds on a Macintosh II at screen resolution. The same colored image was generated in 15 seconds only. Shaded 3-D models are printed in less than three minutes at maximum resolution (300 ppi).

28 F

Phase behaviour of cyclohexane derived from differential thermal analysis and computed by molecular dynamics

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Differential thermal analysis has been used to study the phase behaviours of cyclohexane (C_6H_{12}) and deuterated cyclohexane (C_6D_{12}). Both substances exhibit plastic and non-rotator phases as well as new high-pressure induced phase transitions.

A six-centre Lennard-Jones potential is proposed for cyclohexane and tested by molecular dynamics (MD) calculations. The thermodynamic and transport properties of experimental C_6H_{12} in liquid and solid states were reproduced in acceptable approximation. In particular the phase transition to the high temperature rotator phase (although amorphous) is correctly predicted by the MD calculation. Furthermore the first two reorientational correlation functions of three vectors coinciding with different directions of the molecule have been investigated, from which valuable insight into the rotational behaviour of the occurring liquid and solid phases is derived.

ELECTROSTATIC PROPERTIES OF SOLVATED PROTEINS: A MICROSCOPIC ANALYSIS BASED ON COMPUTER SIMULATIONS

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Molecular dynamics simulations of a small protein barnase in presence of explicit water molecules are described and results from a 100 ps trajectory of the system are analyzed.

The deviations of the average protein conformation from the starting crystal structure is very satisfactory (-1 Å rms for backbone atoms), and the agreement between computed and crystallographic atomic fluctuations is unusually good for portions of the protein that do not participate in crystal contacts. The structure of water around polar and non-polar groups on the protein surface also seems reasonable in that it agrees well with previous observations made in hydrated crystals or in simulations of small solvated molecules.

The thrust of our study concerns the use of the last 25 ps of the generated trajectories to obtain a detailed microscopic description of electrostatic interactions in the protein. Contributions to these interactions from permanent protein dipoles, from orientable solvent dipoles, and from electronic polarizability are evaluated. Although the analysis must still be qualified as preliminary, a number of clear trends emerge. The contribution of water to local fields inside the protein is substantial. It affects field magnitudes and field orientation respectively by 30% and 31 degrees on the average. In comparison, the contribution from electronic polarizability alone is much lower with an average of 6% in field magnitude and 12 degrees in field orientation. But statistical analysis of both contributions shows that they display an appreciable degree of inhomogeneity throughout the protein matrix which suggests that their relative importance may vary according to the local environment.

Modelling of Molecular Structures and
Properties in Physical Chemistry and
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Nancy - 1989

NMR studies of proteins and protein-DNA interactions

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With two-dimensional NMR spectroscopy solution structures of small and medium sized biomolecular systems can be determined. The nuclear Overhauser effects, or NOE's, in the biomolecule are translated into proton-proton distance constraints, which can be used in Distance Geometry algorithms and Restrained Molecular Dynamics simulations to determine the range of possible structures. The accuracy of the distances derived from NOE's can be improved by an iterative relaxation matrix approach. The procedure will be illustrated by the structure determination of DNA octamers and of the protein crambin.

A major bottleneck for determining structures by NMR is the assignment of proton resonances. By performing three-dimensional experiments the resolution can be increased. Some results of non-selective three-dimensional measurements will be shown.

Two-dimensional NOE studies of complexes of *lac* repressor headpiece with *lac* operator fragments are presented, including a 2:1 complex with a 22 basepair operator (total mol.wt. 25.000). A large number of protein-DNA NOE's has been identified. By a combination of molecular docking and Restrained Molecular Dynamics using these NOE's as constraints, models of the *lac* headpiece operator complex were built. An interesting feature of the structure of the complex is that the second ("recognition") helix binds in the major groove of the DNA with an orientation that is approximately 180 ° different from what has been found for othe. DNA binding proteins. The model predicts specific protein-DNA interactions which have been found recently in genetic experiments with the complete *lac* repressor as well.

Protein structure determination using NMR data with energy minimisation and molecular dynamics calculation

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Recent developments in two dimensional NMR spectroscopy allow the structure determination of proteins in solution.

These structures are calculated by a combination of NOESY * determined distances with energy minimisation and molecular dynamics. These distances are introduced as constraints during the calculations.

However, before these methods can be applied, it is necessary to assign the various resonances from the NOE maps to their parent protons.

The M.C.D strategy (Main-Chain-Directed) (1) for assigning these resonances is used.

The quantitative evaluation of 2D maps using the " P.A.R.I.S " (Program for Automatic Recognation and Integration of 2D NMR Signals) (2) provides information of interproton distances smaller than 5 Å.

This approach is illustrated with the toxin from AaH scorpion venom.

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* NOESY: Nuclear Overhauser Effect Spectroscopy.

INFLUENCE OF THE BASE SEQUENCE AND CONFORMATION ON THE STRUCTURE OF THE POLYNUCLEOTIDE HYDRATION SHELL

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The hydration shells in the minor and major grooves of several double helices with different nucleotide sequences and conformations have been studied. The Monte Carlo method (algorithm of Metropolis et al.) was used for simulation of systems containing helical stacks of complementary base pairs and 30 water molecules per each base pair with unidimensional periodic boundary conditions along the axis of the helix. The repeating unit comprised 6 base pairs. The mutual arrangement of the base pairs corresponded to the A and B conformations of poly(dA)·poly(dT), poly(dG)·poly(dC), poly(dA-dT)·poly(dA-dT) and poly(dG-dC)·poly(dG-dC). The average energetic and structural characteristics for the simulated systems at room temperature and at a temperature close to absolute zero were calculated, the patterns of the hydrogen bonded bridges formed by 1,2 and 3 water molecules connecting hydrophilic centres of the bases, are considered and the probabilities of formation of such bridges have estimated. The hydration shell structure depends not only on the nature of the base pair, but on the sequence and conformation although the total hydration characteristics (energy and its components, the number of water-water and water-base H-bonds) depend only slightly on the latter factors. The structural elements peculiar to the hydration shells of the minor and major grooves of helical stacks of base pairs have been found. The probability of formation of one water molecule bridges between the hydrophilic centres was found to increase when the stack transforms from the A to B configuration (one water molecule bridge means that a water molecule forms H-bonds with two or three base atoms). This result is discussed in connection with the water economy concept proposed for the explanation of the B to A DNA transition. The difference in the structure of the hydration shells near NH_2-groups of A:T and G:C pairs was found and discussed.

SIMULATION OF PROTEINS: STRUCTURES, DYNAMICS, & THERMODYNAMICS

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Proteins are one of the essential constituents of living systems so that an understanding of their properties is necessary for a fundamental approach to biological problems. It will be demonstrated that molecular dynamics simulations provide a method for obtaining information concerning protein structure, dynamics, and thermodynamics. Of particular interest are the internal motions which are sizeable in spite of the close packing of the atoms in the native structure; such fluctuations play an important role in ligand binding. The utility of simulations for structure refinement and for determining the properties of modified proteins will be described.

Base Sequence Effects and Transitions in DNA

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Experimental evidence on the biological role of fine structure within DNA is rapidly accumulating. In principle, theoretical modeling should be able to help in deciphering this new "code", however the size and complexity of the molecular systems involved has hindered progress in this area.

Recent developments in our laboratory have led to two new methodologies which should improve the situation. Firstly, we have developed an energy minimisation procedure, specifically oriented to the treatment of nucleic acids, which directly uses helicoidal parameters as variables. We are thus able to describe DNA oligomers with ten times fewer variables than are necessary in classical molecular mechanics. At the same time we are able to study much more easily the energy dependence of structural deformations. Secondly, we have formulated an algorithm for rigorously describing the conformation of irregular nucleic acid oligomers and, in particular, their curvature. Application of these techniques to studying the influence of base sequence on the fine structure, the flexibility and the conformational transitions of DNA will be presented.

ETUDE CONFORMATIONNELLE PAR DYNAMIQUE MOLECULAIRE DE QUELQUES INHIBITEURS DES COLLAGENASES BACTERIENNES.

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Les collagénases bactériennes sont des métalloprotéines à zinc capables de cliver avec une grande spécificité le collagène natif et des substrats de synthèse. Une famille d'inhibiteurs de l'enzyme, de formule générale $HS\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}PRO\text{-}X$ (X= L-aminoacide), a été obtenue. Les constantes d'inhibition mesurées varient fortement avec la nature du residu X.

Les dérivés N-méthylés de X présentent une activité plus grande par rapport au composé parent. Ils sont caractérisés par une réduction de l'espace conformationnel par rapport au composé non méthylé. Deux de ces composés (X = Ala et X = N-methly-Ala) ont été choisis en vue de l'étude par dynamique moléculaire de la restriction de l'espace conformationnel.

Les calculs de dynamique moléculaire réalisés à 600K à l'aide du logiciel CHARMM, ont permis de mettre en évidence l'existence de 3 familles de conformations pour le composé normal et de 2 familles pour le composé méthylé. Les valeurs des barrières de potentiel et des minima d'énergie pour ces différents conformères ont été calculés en géométrie relaxée. La comparaison avec les résultats expérimentaux de la RMN montre la nécessité de la prise en compte dans ces calculs du facteur entropique et des effets de solvant.

Dans ce but, plusieurs sous-programmes ont été développés et intégrés au logiciel CHARMM. Ils permettent de calculer la différence d'énergie libre entre différents conformères à partir de dynamiques moléculaires à 300 K.

La prise en compte du facteur entropique donne un bon accord avec les résultats expérimentaux de la RMN.

Ce travail est poursuivi actuellement pour tenir compte des effets de solvant.

EVALUATION OF ELECTROSTATIC PROPERTIES AT ENZYME ACTIVE SITES.

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Understanding at the atomic level how proteins and their ligands interact is one of the most crucial challenges in the molecular interaction studies. Such an interaction is characterized by an energy E(int) that may be evaluated at different levels of approximation depending on the size of the system and the distance between the interacting partners.

At large distances, the most important component of E(int) is the electrostatic interaction energy E(es). This work attempts to calculate E(es) from valuable expressions of the electrostatic potential (E.P.) at the quantum chemistry level.

In the first part, modelized active sites of alpha chymotrypsin and of native and mutated subtilisins have been investigated in view to point out the electrostatic features involved in the beginning of the interaction. The level of approximation in the derivation of the E.P. factors (density matrix elements, monoelectronic integrals), the influence of the number of residues in the model (from 91 to 277 atoms), as well as the influence of the solvent molecules (from 0 to 25 water molecules) are discussed. The most striking result is the relation between the direction of the high dipole moment value and an impressive E.P. negative well located on one side of the cleft in and around the nucleophilic serine [Proteins, J.L.B. et al, submitted].

The second part of this work proposes a numerical procedure to derive E(es) with a high performance ratio (accuracy level)/(CPU time). This procedure consists in a 3D numerical integration of the product of the E.P. of one partner and the charge density of the other. The approximations involved in this calculation refer to the way the electrostatic potential and the charge density are determined. Numerical ab initio SCF STO-3G(Wls) as well as CNDO type calculations are presented versus analytical SCF STO-3G(Wls) ones. These clearly show that the numerical procedure at the semiempirical level is quite satisfactory as far as the accuracy is concerned, and has the great advantage to be far less time consuming than the ab initio analytical way [Th.Chim.Acta, D.D. et al, accepted].

Theoretical Prediction of Base Sequence Effects in DNA and RNA

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The role of the base sequence in determining the structure of B-DNA is already well established. But little is known about base sequence effects for other conformation such as Z or A allomorphs.

The use of a new molecular modeling methodology, JUMNA, based on internal and helicoidal variables, has allowed us to detect clear effects of base sequence on the conformation of DNA and RNA double helix.

The results we shall present for oligomers with dinucleotide symetry imposed show that, especially within the Z-DNA or RNA family, considerable polymorphism can exist. Certain sequences can adopt more than one conformation. In these cases, the helicoidal characteristics are very different although the energies are very similar. We note that, overall, large changes in base pair positioning require only small coupled changes in backbone dihedral angles.

Comparison between B- and Z-DNA or A- and Z-RNA conformations show that the order of B-Z transition enthalpies generally correlates with the number of syn-purine/anti-pyrimidine errors (i.e. syn-pyrimidine and/or anti-purine).

Finally, we use our molecular modelling for the interpretation of the highly variable experimental chemical reactivities of a natural Z-DNA, in terms of conformational discontinuities.

Modeling DNA Curvature as a Function of Base Sequence

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It is now well known that certain sequences of DNA are naturally curved and that this curvature can play an important role in the biological functioning of DNA. However, today there is still no clear structural explanation for these effects.

We have consequently undertaken a theoretical modeling study in an attempt to better understand how the base sequence can influence the fine structure of DNA. The results presented will show some applications of the programs Jumna and Curves which have been specifically designed for the construction, energy minimisation, manipulation and analysis of nucleic acid oligomers. The use of helicoidal parameters and internal coordinates during energy minimisation is particularly helpful for investigating base sequence effects and DNA flexibility in a controlled way. The rigorous analysis provided by the Curves algorithm enables us to study both natural curvature and to investigate the anisotropy of imposed DNA bending.

MINIMISATION ET DYNAMIQUE MOLECULAIRE DE L'ADN-Z MODIFIE PAR L'ACETYLAMINOFLUORENE

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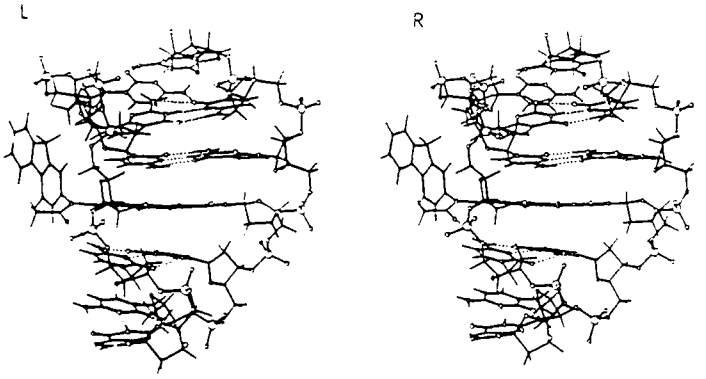
Le programme de mécanique moléculaire AMBER, version 3.0, a été utilisé pour étudier les conformations adoptées par la guanosine modifiée sur la position C8 par le carcinogène acétylaminofluorène (AAF). A cet effet, nous avons introduit dans le programme AMBER une routine permettant d'utiliser une "constante diélectrique" prenant des valeurs entre 1 et 80 ; celles-ci varient de façon sigmoïdale en fonction de la distance, suivant la forme suggérée par Lavery, et al. (J. Biom. Struct. and Dyn.,3,989-1014 (1986)).

Nous avons effectué une minimisation systématique de la guanosine modifiée par l'AAF en fonction de l'angle de torsion autour de la liaison glycosidique et de celui autour de la jonction entre la guanosine et l'AAF. Les conformations optimales ainsi obtenues, compatibles avec la forme Z de l'ADN, ont été insérées dans un hexamère-Z $d(CGCGCG)_2$ et à nouveau minimisées. Les structures minimisées ont ensuite été soumises à un calcul de dynamique moléculaire partielle sur la séquence 5'-C-GAAF-C-3'. Tous ces calculs ont été effectués avec une "constante diélectrique" égale à r, à 4r, ou "sigmoïdale".

Une des conformations préférées aussi bien en minimisation qu'en dynamique est représentée dans la figure stéréoscopique ci-dessous.



RECONNAISSANCE DES BASES DE L'ADN PAR LIAISON HYDROGENE
Effet de la longueur d'une chaîne hydrocarbonée

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OBJET. Une série de dérivés du méthoxy-2 Chloro-6 amino 9 acridine portant une chaîne aliphatique de longueur variable terminée par un groupe carboxamide libre, interagit de manière préférentielle avec un ADN riche en paires (G-C). Cette interaction varie avec la longueur de la chaîne. On estime qu'elle est optimum lorsque le groupe terminal peut former dans le petit sillon deux liaisons hydrogène avec le groupe NH_2 et le N_3 d'une guanine adjacente au site d'intercalation.

RESULTAT DES CALCULS. Le calcul par SIBFA de ces dérivés de l'*acridine intercalés dans un hexamère rigide formé de paires* de bases (G-C) montre que la formation d'un complexe bidenté n'est pas indifférent à la séquence : ils se forment dans une séquence $(GCCGGC)_2$ mais pas dans $(CGCGCG)_2$.

Pour ces complexes bidentés l'énergie d'interaction stabilisante est la plus importante pour le composé comportant 5 méthylènes, ce qui est conforme à l'expérience.

De même la différence entre l'énergie totale du complexe et l'énergie du ligand seul étendu indique que la stabilisation est maximum pour l'isomère à 5 méthylènes. La comparaison des énergies des complexes pour des séquences d'hexamères $(GCCGGC)_2$, $(ATTAAT)_2$ et $(TATATA)_2$ préserve le caractère favorable pour le même composé.

On peut noter cependant que ces séquences particulières sont insuffisantes pour rendre totalement compte des faits expérimentaux.

MOLECULAR MODELLING OF TWO DOUBLE STRANDED DNA FRAGMENTS TGACGTCA and ACTGCAGT

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Footprinting experiments showed that the antitumour drug N-methyl 9-hydroxy ellipticine (NMHE) preferrentially binds to CG sites in double stranded DNA, and led to the determination of a consensus sequence ACGT (B. RENE and co-workers).

To elucidate this selectivity, we have carried out the ^1H NMR study and the molecular modelling of the binding of NMHE to a DNA octamer containing the consensus sequence - TGACGTCA -, and its inverse sequence ACTGCAGT. The two fragments have first been studied without the drug.

On the basis of these NMR data, we undertook the molecular modelling of the octamers.

From the coupling constants J1'2', J1'2", J2'3', J2"3', measured from COSY experiments, we have considered each sugar ring as the result of an equilibrium between the C2'-endo and the C3'-endo conformations, which can be represented by the percentage of C2'-endo form (Rinkel and Altona 1987).

Thus for both molecules a set of $64 = 2^6$ starting structures were generated, considering for each sugar ring (except those at the extremities) the C2'-endo and C3'-endo conformations. Those models were refined, without constraining the geometry of the deoxyribose. We selected the best ten ones in terms of energy (with less than 5 kcal difference between one another). We calculated the coupling constants of our models and confronted them to the experimental constants. We considered each nucleotide independently. For some of them, the calculated couplings were in good agreement with the experimental ones (pure C2'-endo). For the other ones we had to consider the equilibrium C2'-endo - C3'-endo, i.e. taking the C2'-endo form of one sugar, we tried to find another structure where the same sugar exists in the C3'-endo conformation, and a fraction p such as, for the 4 couplings :

$$p.J_{C2'endo} + (1-p).J_{C3'endo} = J_{exp}$$

We ruled out the structures for which it was not possible to find such a fit for all nucleotides. Thus we kept 3 models.

Then interproton distances were used for the final determination of the structures.

The work concerning the binding of the drug to the fragments is currently being done.

NUCLEOTIDE MISPAIRS STABILIZED BY WATER BRIDGES. MODELING OF STRUCTURE AND ROLE IN TEMPLATE BIOSYNTHESIS

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To elucidate the mechanisms of wobble in codon-anticodon interaction and of errors in template biosynthesis of nucleic acids, the possibility of insertion of water molecules into wobble nucleotide pairs was considered. At the first step the calculations of intermolecular interaction energy for systems containing two bases and one or two water molecules were carried out by the method of atom-atom potential functions. There exist energy minima for each base pair, corresponding to a single N-H...O or N-H...N H-bond between the bases and H-bonding of the water molecules with both bases. In the other minima, where two bases are connected via two H-bonds, water bridges additionally stabilize such pairs. The position of the bases and water molecules of some calculated complexes correspond to those of nucleotide pairs in some double-helical oligonucleotides, as known from X-ray and NMR data.

At the second step we have attempted to insert these pairs into the third position of the codon-anticodon complex under the assumption that the rearrangement of the sugar-phosphate backbone, that is necessary for such a pair formation, occurs only in the anticodon, but three nucleotides of codon during codon-anticodon recognition have the fixed conformation of A-RNA. Consequently, along with the standard pairs the following pairs become probable: UG, UI, UU, CU, GU and AI, GU and AI being weaker than the other ones. All other pairs appear to be sterically impossible. Atom-atom calculations of the system (codon-anticodon loop - water molecule) established the energy minima for every permitted wobble pair and revealed that the conformational rearrangement of the anticodon loop which accomodates the latter for each of these pairs is fairly small and so quite possible. All the conclusions are in good agreement with the experimental data.

STUDY ON THE SEQUENCE SELECTIVITY OF THE BI-FUNCTIONAL INTERCALATOR DITERCALINIUM

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ABSTRACT

The structures and binding energetics of the complexes formed between the rigid linking chain DNA bi-functional intercalator ditercalinium (1) and a series of model tetradeoxynucleotide duplexes that follow always an alternating purine-pyrimidine sequence have been investigated by means of JUMNA (2), a molecular mechanics approach. The ditercalinium complexes all contain one internal excluded site such that two base pairs are sandwiched between the chromophores intercalated at the terminal sites.

A comparative energy analysis of all the complexes has permitted us to order them according to their base pair preference. The energy minimisation calculations using the JUMNA methodology point to an increased stabilisation of the minor groove complex (i.e., the complex in which the piperidine rings of the linking chains of the drug occupy the minor groove side) over the corresponding major groove complex in the case of d(ApTpApT)2. All other complexes are major groove complexes. These results put forward the many-sidedness of the modes of intercalation of ditercalinium. We have, in addition, characterised quantitatively the local deformations induced by the drug on the DNA fragment.

The prediction in the case of the ATAT sequence is in agreement with the theory of the negative molecular electrostatic potential of the DNA minor groove proposed by Pullman, Lavery and coworkers.

(The mode of intercalation of ditercalinium with the ApTpApT sequence is presently being investigated in this same laboratory by ^{1}H and ^{31}P NMR techniques.)

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DNA Bis-Intercalation in the 7H pyrido [4,3-c] carbazole family : A comparative ^{1}H and ^{31}P NMR study.

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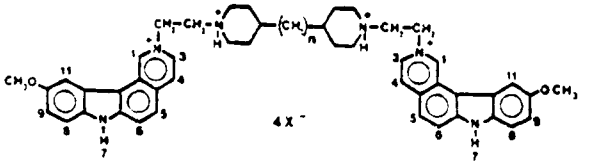
Ditercalinium (2,2'-{[4,4'-bipiperidine]-1,1'-diyldi 2,1 ethane diyl}bis[10-methoxy - 7H pyrido [4,3C] carbazolium]tetramethane sulfonate) (NSC 366241) a DNA bis-intercalating compound, is a potent antitumoral rigid dimer. Previous studies (1) have shown that a reduced flexibility of the linking chain of such dimer is essential for its biological activity. In order to understand at the molecular level the mechanism of action and the structure-activity relationship of these series of DNA intercalators, new dimers with additional methylene groups between the two piperidine rings have been synthesized (2). Addition of one methylene group in the chain preserved the activity, whereas addition of two methylene groups reduced the cytoxicity which finally disappears when three methylene groups are inserted. Therefore, the study of the interaction of dimers bearing no (202) two (222) and three (232) methylene groups with the self complementary hexanucleotide $d(CGATCG)_2$ have been investigated by ^{1}H and ^{31}P NMR.

The results indicate that all dimers bisintercalate into the DNA and exhibit a neat preference for pyrimidine-purine sequences. The intermolecular NOE effects between the dimers and the nucleotide lead to the conclusion that the three dimers intercalate with their rigid bis-ethyl bispiperidine chain fitting the major groove of the helix. Inter-residue NOE effects at the DNA level, as well as induced shifts are discussed in relation to both the conformational changes induced on DNA upon intercalation and to the different activity of the dimers.



n = 0	202
n = 1	212
n = 2	222
n = 3	232

PELAPRAT, D., DELBARRE, A., LEGUEN, I., ROQUES, B.P., LE PECQ, J.B., (1980) *J. Med. Chem.* **23**, 1336-1343

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BIS-INTERCALATION OF DITERCALINIUM AND "FLEXIBLE" ANALOGUE IN THE OCTANUCLEOTIDE d(TpTpCpGpCpGpApA)2: A COMPARATIVE STUDY BY NMR AND MOLECULAR MODELLING

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7H-Pyrido [4,3]c carbazole dimers of the ditercalinium family are DNA bis-intercalators that display high DNA affinity and antitumor properties. The latter depends on substitution on the pyridocarbazole rings and/or "flexibility" of the linking chain. When the two piperidine rings of ditercalinium (figure I a) are replaced by six methylene groups (as shown in figure I b), the drug cytotoxicity desappears.

The interaction of Ditercalinium and its "flexible" analogue with both the tetranucleotide d(CpGpCpG)2 and the octanucleotide d(TpTpCpGpCpGpApA)2 has been therefore investigated by ^{1}H and ^{31}P NMR. The octanucleotide was chosen as it has only one site available for bis-intercalation, and is long enough to probe long distance perturbations.

The results indicate that all dimers bis-intercalate into the DNA via the major groove with similar geometry but with substantial differences at the DNA level, particularly in the sugar-phosphate backbone.

In addition, molecular modelling calculations are being carried out on these complexes and compared to the models obtained from NMR data.

DYNAMIQUE MOLECULAIRE POUR LA SIMULATION DE REACTIONS DONT LA CINETIQUE EST LIMITEE PAR LA DIFFUSION

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Les constantes de vitesse apparente d'un grand nombre de réactions en phase liquide sont affectées par les phénomènes de transport moléculaire. De nombreux modèles, toujours fondés sur l'hypothèse d'un solvant considéré comme un continuum, ont été proposés pour expliquer de tels phénomènes. Ils présentent tous des imperfections, plus ou moins flagrantes suivant le type de système moléculaire considéré.

L'expérimentation directe est, bien sûr, la seule possibilité d'établir leur validité. Mais elle n'est pas toujours réalisable, à cause, soit d'une précision insuffisante, soit du choix d'un système moléculaire adapté. De ce point de vue, la dynamique moléculaire fournit des "expériences théoriques" et de précieux renseignements sur la validité des concepts, même s'il s'agit d'une méthode un peu lourde et coûteuse, ne pouvant suppléer aux modèles "continus" lorsqu'on veut interpreter des résultats expérimentaux.

Un calcul de dynamique moléculaire a été entrepris pour étudier ces réactions dont la cinétique est limitée par la diffusion moléculaire. Toutes les molécules du milieu considéré (solvant et molécules réactives) sont supposées sphériques, de taille identique, la réaction se produisant dès le premier contact (hypothèses de SMOLUCHOWSKI). Nos premiers résultats montrent l'existence d'effets transitoires non prévus par les modèles continus, permettant d'expliquer en partie, par exemple, les écarts observés, dans les graphes de STERN VOLMER, lorsqu'on excite de façon continue (c'est à dire en intégrant tout le déclin) ou pulsée (c'est à dire en essayant de résoudre temporellement le déclin).

De telles simulations peuvent maintenant être entreprises dans le but de décrire des systèmes plus complexes (tailles différentes pour le solvant et les molécules réactives, réactivité non uniforme, potentiels locaux, etc...).

Structure and Dynamics of Water and Ionic Solution near Biomembrane Surfaces from Molecular Dynamics Simulations

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The interface between a biomembrane surface and liquid water (or ionic solution) is studied with molecular dynamics simulation technique. Therein the membrane surface is modeled by COO^- groups and a TIP4P model is used for water molecules. Strong ordering of the water molecules close to the membrane is found. Ions influence this structure as well as that of the surface. The ion transport from the bulk phase towards the membrane surface is studied.

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TRANSPORT DANS LES MEMBRANES BIOLOGIQUES

MODELISATION ET EXPERIENCES

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L'étude des membranes biologiques et plus particulièrement de la dynamique membranaire fait appel à différentes techniques physiques d'investigation, qui permettent de caractériser soit un paramètre d'ordre, soit les propriétés de transport en terme de coefficients de diffusion latérale.

Pour des systèmes modèles simples (soit des phospholipides purs, soit des mélanges constitués de phospholipides additionnés de protéines membranaires purifiées) nous avons, à la fois, réalisé des expériences et une modélisation qui mettent en évidence un rôle d'obstacle de la part des protéines sur les propriétés de transport dans les membranes.

L'expérimentation repose sur l'emploi de trois techniques complémentaires, la fluorescence résolue dans le temps (inhibition de la fluorescence du pyrène), la RPE (nitroxydes : 5 et 16 NS) et la calorimétrie différentielle.

La modélisation, qui tient compte de concepts de physique des liquides pseudo-bidimensionnels, permet de simuler les propriétés de transport au sein des membranes et de prévoir l'effet des protéines.

A SIMPLE MODEL OF NUCLEIC BASES ASSOCIATION : THE CYCLIC DIMER OF THE 2-PYRIDONE VIBRATIONAL STUDY

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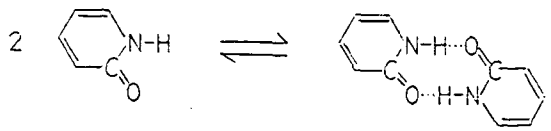
Vibrational spectroscopy, specially ultraviolet resonance Raman spectroscopy, is often used to study nucleic bases association or tautomerism, nucleic acids structural changes or nucleic acids interaction with proteins, metal ions or drugs [1]. For such studies, it would be of interest to correlate the frequency shifts or the intensity variations of the lines to the association state of the nucleic bases.

As simple model system we have chosen the equilibrium between the 2-pyridone monomer (M) and the dimer (D) of this molecule :



M D

By infrared spectroscopy, we have found the concentration range giving nearly the same intensity of monomer and dimer $\nu_{C=O}$ bands directly involved in hydrogen bond association [2] namely $\sim 2.10^{-1}$ M in CH_3CN or CD_3CN and $\sim 10^{-3}$ M in $CHCl_3$ or $CDCl_3$ solutions.

In the present work we try to assign the secondary effects of hydrogen bonding on heterocyclic ring leading to distinct frequencies for the monomer (free 2-pyridone) and for the dimer (associated 2-pyridone).

Previous work on pyridinium, pyrazinium or pyrimidinium salts [3] or on 2-pyrimidone and 2-pyrimidone salts [4] have shown that some ring frequencies are sensitive to the bonding of an hydrogen atom to nitrogen (NH or NH^+). With respect to the spectra of the solid, for 2-pyridone solutions, some bands appear as doublets. The relative intensities of each component of these doublets vary with concentration. Then, the spectral changes are related to the evolution of the $2\,M \rightleftharpoons D$ equilibrium. Infrared spectra of 2-pyridone solutions (2.10^{-1} M in CD_3CN) show such doublets at 1475-1472, 1376-1367, 731-724 and 518-510 cm^{-1}. The components of these doublets are assigned to monomer and out of phase motion of the dimer. We use also Raman spectroscopy in order to identify the in phase motion of the centrosymmetric dimer.

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Simulation of Polyionic Interactions by Progressive Approximations

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Computer generated ionic site correlation functions applied to polyionic macromolecules were analyzed in order to obtain information about the relative probability of polyionic interactions. It is shown that this approach permits predictions about preferred mutual orientations of polyions and could thus be used as guide for estimating the most probable path of approach of interacting charged particles as well as the conformation for ionic complexes, which corresponds to that of the lowest electrostatic free energy. The method of progressive approximations can be applied step-wise to electrostatic interactions and then for greater detail to the analysis of the effects of dielectric phenomena, electric polarization or other short-range molecular forces, again in a step-wise manner. Application of the analysis to highly charged model systems has shown that it is possible to select geometric correlations between alternative polyionic conformations by neglecting most of the short-range molecular forces. The results obtained suggest, that the effects due to solvent interactions, counterions and electric polarization are dominated by long-range electrostatic interactions as far as overall conformational adaptation is concerned, when the molecules,taking part in the interactions, are highly charged species.

The type of site correlation function to be used to estimate the strength of the molecular interactions depends quite naturally on the type of interacting sites investigated: van der Waals interactions are estimated from functions of the type f(1/R^6), interactions in the presence of counterions from f(1/(Rij*exp(K*Rij))), the electrostatic interactions from the strength of the electrostatic field, i.e. f(1/(Rij*Rij)) etc., where R and Rij are the interatomic distances and K) the Debye-Hueckel parameter.

In Fig. 1 plots of 1/(R*R) are shown for a moving polyionic probe and a fixed polyion in a coordinate system. The fly-by correlation curves show alternating maxima of repulsions and attractions and permit the pairwise alignment of the molecules corresponding to their interaction maximum. Since the geometric information content derivable from such fly-by correlation curves does not depend very much on the value of the exponent of R, the structural deductions that may be drawn from such analyses do not depend very much on the exact type of correlation function chosen. This alignment determines, in this particular example, the position of the diad axis of symmetry of the polyionic dimer.

The method of analysis has been applied to complex, highly charged macromolecules, like for instance histones, the basic nuclear proteins, as well as acidic polynucleotides like DNA. Thus, it has been possible to suggest a self-consistent, high-resolution molecular model for chromatin subunits (1).

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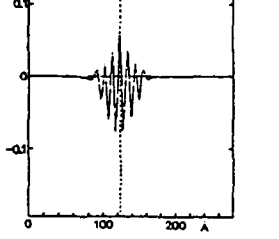

Figure 1
Fly-by correlation curve of an artificial polyion, polyalanine (Ala)50 with blocked ends and Glu19,26,33,40,Arg22,29,36,43, designed to mimic the central segment of histone 4.

INHIBITOR AND SUBSTRATE BINDING AND CATALYSIS IN DIHYDROFOLATE REDUCTASE - A THEORETICAL APPROACH

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A fundamental problem in chemistry and biochemistry of proteins is understanding the role of a single amino acid residue in determining the molecular properties of the protein. Site-specific directed mutagenesis is a very powerful approach which yields experimental data such as changes in catalytic properties for mutant species of enzymes compared with their native analogues. Still more understanding can be obtained of an enzyme system if the X-ray structures of the parent and mutant enzymes are solved. E.Coli dihydrofolate reductase (wild type, Ser 27 and Asn 27 mutants) is such a system and experimental data from (1) - the X-ray structures, binding constants of methotrexate inhibitor (MTX) and catalytic activity for substrate dihydrofolate - were used as a basis for our theoretical study.

A novel methodology consisting of a combination of ab initio split valence basis set calculations and the thermodynamic integration method implemented with the molecular dynamics was used to determine the binding constants and activation energetics of the inhibitor and substrate, respectively. The results obtained support the view that the electrostatic forces play a major role in enzyme catalyses.

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Relationship between molecular properties of some Photosystem II herbicide and their activity on triazine-resistant and susceptible chloroplasts.

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Herbicides such as urea, amide, uracil, s-triazine and methylthiopyrimidine herbicides inhibit the photosynthetic electron flow by competing with a plastoquinone molecule for binding at a common site on the secondary electron acceptor of Photosystem II, formed by the D1 protein.

The conformations and electronic properties of several of these compounds, representative of different structural families active on the same site, were determined using molecular mechanics (CHARMM, SYBYL) or quantum semi-empirical (MNDO, AM1) methods. Dihedral angles, rotational energy barriers, dipole moment and ionisation potential were calculated. Spectroscopic measurements of the *in vitro* hydrogen bonding and charge transfer capacities of these compounds were also carried out and compared with the calculated charge densities. Results obtained by AM1 were found to be the most consistant with experimental data and this method was used to study the hydrogen bonding properties of the carbonyl of ureas or the ring nitrogens of triazines with different proton donors.

The conformational and electronic properties of the inhibitors studied are then discussed in terms of their mechanism of action on the D1 site and its modification by mutations in D1 leading to different forms of herbicide resistance.

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ETUDE STRUCTURALE COMPARATIVE D'HYDROXY ET DE METHOXY FLAVONES. COMPARAISON ENTRE LES RESULTATS RX ET DIVERSES METHODES DE MODELISATION MOLECULAIRE.

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Les flavonoides sont une classe de composes frequemment rencontrés dans les plantes. Ces composes, avec leurs analogues synthetiques sont biologiquement actifs. Nous nous sommes interesses aux effets conformationnels des interactions entre le cycle phenyle et le systeme heterocyclique chromone.

Les etudes RX de trois flavones methoxylees (la 3-methoxy, la 2'-methoxy et la 2',6'-dimethoxy) mettent en evidence une torsion du cycle phenyle variant de quelques degres pour la 2'-methoxy à 70,7° pour la 2',6'-dimethoxy flavone.

Diverses methodes de modelisation moleculaire, de type quantique (MNDO, AM1) et de mecanique moleculaire (MM1) montrent que la methode AM1 de M.J.S. Dewar donne les resultats les plus proches de ceux de l'etat cristallin. La generalisation aux flavones polymethoxylees contenues dans les *Citrus* permettra d'envisager des correlations structure-activite.

Structure determination from NMR using a relaxation matrix approach and stereospecific assignment procedures; application to the solution structure of crambin.

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An important problem in structure determination using 2D NMR data is the accurate evaluation of distance constraints from observed proton-proton NOE cross peaks. Ideally, the distance can be derived from the initial buildup rate of NOE intensity as a function of the mixing time used in the NMR experiment. Since at small mixing times the intensity is also small, the initial rate cannot be measured directly. At longer mixing times, however, magnetisation transfer from or to other neighbouring protons (the so called spin diffusion) has to be taken into account. We describe the Iterative Relaxation Matrix Approach (or IRMA procedure), which handles spin diffusion quantitatively by solving the Bloch equation for the NOE magnetisation transfer simultaneously for all spins in the system. After combining experimental and theoretical NOE intensities (the latter being derived from a model structure), the relaxation matrix describing the kinetics of the problem is constructed. From this the spin-diffusion corrected constraint distances can be derived directly. Using restrained Molecular Dynamics an improved structure is calculated, which in turn is used to derive an improved relaxation matrix. The whole procedure can be repeated until all experimental NOE's are explained satisfactorily. Theoretical NOE's, i.e. cross-peak intensities predicted on the basis of a structural model, can also be used for stereospecific assignment of proton pairs which are otherwise difficult to discriminate, e.g. B1/B2 protons and terminal methyl groups in Val and Leu. It will be shown how these assignment procedures can be implemented, and how they can be combined with structure optimizations in which the barrier to interchange of the equivalent protons has been reduced to zero. Strategies for the optimization of structures with Distance Geometry and restrained Molecular Dynamics are discussed, using the solution structure of crambin, a protein with 46 residues, as an example.

COMBINED USE OF NMR AND RESTRAINED COMPUTER SIMULATIONS FOR THE MODELING OF THE CYCLIC ANTIFUNGAL LIPOPEPTIDE : STENDOMYCINE.

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For determining the three dimensionnal structure of a molecule in solution, the most powerful method is based on measurements of proton-proton nOe's. Because this mechanism is strongly distance-dependent, nOe's can be translated into proton proton distance used as constraints in additional energy term in computer simulations.

But, translating nOe's in term of distances is not always unambigous due to internal molecular motions and and spin diffusion phenomena.

Refinement structures based on the superposition of the experimental and calculated n0e's intensity matrices seems a better strategy than the fitting of the estimated and calculated distances matrices to take account of all the protons proximities.

This refinement method is applied to the conformational analysis of a cyclic peptide, stendomycine, an antifungal lipopeptide.

MOLECULAR DYNAMICS STUDIES OF PRISTINAMYCIN II_A : FROM CRYSTAL STRUCTURE TO CONFORMATIONS IN APOLAR SOLVENT USING NMR DATA.

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Pristinamycins I and II are natural antibiotics, first isolated from *Streptomyces pristinaespiralis*. These two groups of molecules are chemically different, as PI is a peptidic macrolactone and PII an olefinic macrolactone, but they biologically act in a synergic way. Each group contains several closely related molecules; PII_A is the major component of PII.

An hemisynthetic work has been realized by Rhône-Poulenc Santé to find active water-soluble Pristinamycins. At the same time, crystallographic studies of these two families were initiated.

In the present work, the conformation of PII_A in $CDCL_3$ was determined using restrained molecular dynamics simulations with the help of proton/proton distance constraints obtained by 1D and 2D NOE spectroscopy at 400 and 250 MHz.

The software package INSIGHT/DISCOVER, the programs MANOSK & Chem-X were used. The structure thus obtained was compared to the X-Ray crystal structure previously published (F.Durant & al.,Cryst.Struct.Comm.,1974,3,503-510).

Etude conformationnelle de la tête polaire de l'Amphothéricine B à l'état isolé ou en présence de molécules d'eau.

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Il existe de nombreuses études expérimentales de l'activité des polyènes ionophores et de leur sélectivité antifongique. L'activité ionophorique des polyènes est due à la formation de complexes avec les stérols. La stabilité des complexes polyènes-stérols est fondée sur l'énergie de deux types d'interaction et de liaison:

1. les liaisons hydrogène entre groupements polaires du polyène et l'hydroxyle stérolique et éventuellement quelques molécules d'eau.

2. des liaisons Van der Waals entre la partie heptaènique du polyène et le squelette steroïdique.

Selon la structure de la tête polaire du polyène, l'énergie de la liaison hydrogène est très variable: si elle est forte, le complexe ionophorique est stable quel que soit le stérol; si elle est faible, les interactions de Van der Waals deviennent prédominantes et il y a alors sélectivité vis à vis des différents stérols.

Une étude préalable de la structure de la tête polaire à l'état isolé, ou en présence de molécules d'eau, est indispensable avant l'étude des différents complexes. Nous avons effectué des calculs par la méthode SIBFA: selon ce procédé, la "macromolécule" est considérée comme un ensemble de fragments reliés par de simples liaisons et la variation d'énergie intramoléculaire est le résultat d'une somme d'énergies d'interaction entre les fragments. La distribution de charges de chaque fragment est obtenue à partir d'une décomposition multipolaire d'une fonction d'onde ab initio.

51 B

Modelization of the disulfure bridge in Proteins : *ab-initio*-CI studies of S_2H_2 and $S_2(CH_3)_2$

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The conformation of the disulfide bond in proteins plays an important role in their properties[1]. Much theoretical work has been done concerning the rotationnel barriers about the S-S bond. In this work, we investigated not only the fundamental state potential surface but also that of the first excited state, in order to investigate the possible radiation damage to the proteins.

We used two models for the disulfide bond the S_2H_2 and $S_2(CH_3)_2$ systems and we will report the potential surfaces around the S-S bound for both of them in the fundamental and first excited state.

All calculations were done with the HONDO programm [2], using a 4-31G* basis at the CI level.

The disulfide bonds are known to exhibit strong circular dichroïsm. We will also report calculations of the rotatory strengths and dipole strengths of these systems in the virtual orbital approximation. We demonstrate the possibility of using inner-shell electronic spectroscopy in the soft X-ray range to gain access to the absolute conformation around the disulfide bond in proteins from the circular dichroïsm.

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QCPE Bull., 8(2), pp.79-82 (may 1988)

Analysing and Modeling the Deformation of Protein Secondary Structures

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Secondary structures, most notably, alpha helices and beta sheets form a considerable part of most protein conformations. However, these structural elements rarely approach perfect helicoidal symmetry and their participation in the overall conformation often involves considerable deformations. In order to attempt to understand the energetic nature of these effects we have made two types of investigation.

Firstly, using a new algorithm we have analysed the nature of the deformations occurring in well resolved protein structures, notably the bending of alpha helices and the bending or torsion of beta sheets. Secondly, we have made theoretical calculations of deformation energy using a methodology which enables us to control easily the overall conformation of oligopeptide fragments. We attempt to correlate the findings with the influence of the peptide sequence and to clarify, in particular, the role of special residues such as proline.

Describing Protein Conformation: A New Mathematical Approach

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Although a considerable number of protein structures have now been crystallographically determined to high resolution there are still difficulties in extracting all the conformational data that these results contain. In particular, there is no rigorous procedure for the precise location of secondary structures and the description of their deformations, or for determining the exact pathway followed by a folded polypeptide backbone.

An algorithm, P-Curves, recently developed in our laboratory enables these goals to be achieved in a clear and general way. This approach corresponds to a generalized helicoidal description of protein structure and yields both an overall axis describing the folding of the protein backbone and a full set of helicoidal parameters locating each peptide in space. The analysis of a number of well resolved protein conformations subsequently allows us to define the extent of regions of secondary structure without reference to local, and often subjective measures, such as hydrogen bonding or phi/psi angles. This data also allows easy comparison of homologous protein conformations and should facilitate the definition of sequence-structure correlations.

TAUTOMERISM OF THE NUCLEIC ACIDS BASES REVISITED: FROM ISOLATED (NON-INTERACTING) BASES TO THEIR COMPLEXES

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Results are presented from the recent *ab initio* quantum-mechanical studies of the relative stabilities of the isolated (non-interacting with the molecules of an environment) tautomers of the nucleic acids bases. Calculations predict that the "rare" tautomers (important for tautomeric mechanism of point mutations) are higher in energy than the "normal" tautomers by 60-65 kJ/mol for adenine and thymine (uracil), but only by 7-8 kJ/mol for cytosine, while in the case of guanine its rare tautomer is lower by 3 kJ/mol than its normal tautomer. The predictions correlate well with recent experimental findings from the infrared spectroscopic studies of the bases isolated in inert gas matrices.

Results are also presented from the combined approach (*ab initio* calculations for relative stabilities of the isolated tautomers together with a calculation using Claverie's method for predicting intermoloecular interaction energies) applied for study the energetics of dimers and complexes consisting of different tautomers of cytosine and guanine. It is shown that the interactions between the bases change the relative stability of the individual tautomers, particularly "discriminating" against the dimers (complexes) containing the rare tautomers. These intermolecular interactions may be an important factor involved in the complicated control (repairing) systems of living organisms, which discriminates against the rare (non-canonic) tautomers of the bases during several biological processes.

ELECTROSTATIC BASIS FOR PROTEIN FUNCTIONS: INCORPORATING THE ENVIRONMENT IN MICROSCOPIC CALCULATIONS OF FREE-ENERGY AND DYNAMICS OF CHEMICAL PROCESSES IN SOLUTIONS AND PROTEINS

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It has been argued repeatedly that electrostatic free energies are the key factors that correlate structure and function in proteins.[1] However, the examination of this hypothesis is somewhat meaningless without the ability to perform microscopic calculations of enzymatic reactions and related processes. Our developments in this field during the last 15 years will be reviewed. This will cover solvent models ranging from the simplified, yet microscopic, Langevin Dipoles model[(1,2)] to surface constraint all atoms models which were implemented with free energy perturbation calculations.[(1,3)] The incorporation of microscopic solvent models in quantum chemical calculations will be considered, discussing the relative advantages of MO-SCF approaches[(2)] and Valence Bond approaches.[(3,4)] The implementation of such methods in calculations of activation free energies in solutions and proteins will be described.[5-7] The role of the electrostatic fluctuations of the solvent in controlling dynamical effects will also be discussed and the evaluation of dynamical effects in quantum chemical calculations of charge transfer reactions will be outlined.

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MONTE-CARLO FREE ENERGY CALCULATIONS IN CONFORMATIONAL STATISTICS OF POLYPEPTIDE CHAINS

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Entropy and more precisely free energy are the relevant quantities, besides the commonly evaluated conformational energy, for the theoretical study of macromolecular systems especially when they are subject to solvent effects. But there is generally no direct access to such quantities because of convergence problems in conventional Monte-Carlo simulations. Moreover, even if it is clear that short-range interactions restrict chain units to a limited number of low energy conformations, one has to considere actually excluded volume, long-range electrostatic interactions and solvent effects as main factors for analysing the folding of molecular chains into stable conformations. However, the introduction of such long-range effects in calculations is a source of major difficulties as one can no more express the conformational energy as a sum of terms associated to chain units or first-neighbor pairs.

However, the partition of the total conformational energy of a chain molecule into short-range and long-range interactions allowed us to propose an effective new approach(1) for using Monte-Carlo calculations in statistical mechanics of molecular chains. The calculation method in which the part of energy coming from short-range interactions is not recalculated at each step of the procedure, is based on the use of statistical weight matrices for short-range terms and importance sampling for the part of energy associated to long-range interactions.

Such an approach gives also a way of defining all the statistical properties for reference states of the molecular system. Therefore, it becomes possible to study the behavior of the molecule under more complex conditions(2). The free energy and entropy variations due to long-range interactions are then calculated. Moreover, solvent effects can be introduced by simple modifications of long-range terms of the conformational energy as it is generally done for a potential of mean force. Beside the determination of thermodynamic properties of the chain molecule, probabilities of chain units being in their different conformational states are also estimated. This gives finer information on the conformations of chain molecule. Application of these calculation methods are made on molecular models of peptidic hormones.

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Dielectric screening in proteins

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Abstract

We have investigated theoretically the role of dielectric screening in the interaction of proteins with their substrates.

The local polarizability should vary throughout a protein in such a way as to contribute to its activity. To test this hypothesis, we use a standard microscopic model to describe the protein's dielectric properties, and calculate theoretically its susceptibility in response to a set of external point charges. The microscopic model describes the *electronic degrees of freedom* by a set of *atomic* point polarizabilities and the atomic positional degrees of freedom by normal mode dynamics.

Computer programs implementing the model have been developped and incorporated into the Charmm molecular mechanics package (Brooks et al, 1983). Numerical calculations have been carried out on several systems (model alpha helices, cytochrome c, the disk of protein of tobacco mosaic virus), which tend to confirm our initial hypothesis (Simonson et al, 1989).

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Simonson, T., Perahia, D. and Bricogne, G. (1989). J. Mol. Biol., in press.

Calculation of the Free Energy of Intercalation

by

B.M. Pettitt

Graphite intercalation compounds (or the synthetic metals) have many uses in materials science and catalysis. A statistical mechanical theory is developed and applied to study the structural effects that the thermodynamic state of alkali ions have on graphite intercalation compounds. The system considered is that of second stage Rb-graphite. Two dimensional diffraction patterns are computed and compared with experimental measurments. Sensitivity to model parameters are considered. A low order density functional expansion is found to adequately describe the interionic structure and free energies of the system modeled as a two dimensional one component plasma in an anisotropic external field. Work in progress on extensions to molecular cases and the calculation of interlayer free energies aree also presented.

Artificial Intelligence in the Molecular World

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Abstract :

While solving problems is a long tradition in experimental sciences, research on how people actually solve problems is relatively recent. It was supposed twenty years ago that people knew how to perform problem solving and overall knew how to teach their methods.

This subject has been recently deepened in the frame of cognitive sciences, namely by knowledge psychologists and now by knowledge engineers, inside "Artificial Intelligence" (AI). AI is a branch of advanced information processing dealing with these activities which characterize human behaviour : knowledge acquisition and structuration, reasoning, perception, decision making, etc. AI methods, tending to formalize human knowledge and reasoning processes, give us new tools for a better understanding of such processes.

Nowadays, while the use of computers is increasing, the amount and the complexity of the data involved in the different domains of chemistry make it imperative to discriminate which information is relevant and to consider new ways of processing it.

Various aspects of AI may concern the molecular world : knowledge and reasoning representation, heuristic problem solving, planning, image and natural language understanding, knowledge-based and expert systems, "intelligent" computer-aided education, symbolic learning. These aspects will be discussed, focusing on the specific problems the chemist or physicochemist has to face with (synthesis, experimental planning, structure elucidation, spectra interpretation, classification, information retrieval, fault diagnosis in analytical instrumentation, student education and so on).

ION CHANNELS IN BIOMEMBRANES

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IONIC EFFECTS ON BIOMOLECULAR CONFORMATION

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The structures and structural transitions of polyionic biomolecules (e.g.DNA,RNA) are strongly affected by their interactions with water and ions.I briefly review the main experimental facts and discuss the PMF (potentials of mean force) theory which yields a quantitative description of ionic effects on the B-Z ,B-A,and helix-coil transitions of DNA.Using this theory one can also compute the vibrations of charged molecules in simple electrolytes and estimate the three dimensional distributions of the ions around complex polyionic structures.Recent results will be presented.

MOLECULAR MODELLING IN BIOLOGY,

with or without QUANTUM CHEMISTRY.

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Many people seem to ignore to what an extent the consideration or the omission of certain fundamental quantum-chemical concepts has played a decisive role in the success of some and the failure of others in achieving basic discoveries which laid the foundations of molecular biology.

Today when modelling procedures strive towards the elucidation of complex structures and interaction mechanisms the necessity of continuing to use quantum mechanical concepts and methods is even greater than before. The insufficiency of molecular graphics based solely on qualitative considerations of geometrical fitting, hydrogen bonding capabilities, and similar pictorial representations, will be illustrated in the topical efforts of the search for antituor DNA binding ligands with selective specificity for the minor groove of AT or GC base-pair sequences.

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MODELLING OF MOLECULAR STRUCTURES & PROPERTIES
44th Intern.l meeting of Physical Chemistry

CHANGES IN THE PROGRAMME

NEW CONTRIBUTIONS

23 A - **Système OCTANG: un nouveau descripteur 3 D polyvalent**
E.DELANCE, J.P.DOUCET et J.E.DUBOIS - ITODYS - 1 r.Guy de la Brosse, Paris

38 C - **Molecular Modelling of Two Double-Stranded DNA Fragments TGACGTCA and ACTGCAGT** - J.M.PIRIOU, O.MAUFFRET, S.FERMANDJIAN, M.LE BRET, J.ARMIER° Inst. Gustave Roussy, Biochimie-Enzymologie et ° Inst. de rech. scientifique sur le cancer

41 A - **DNA bis-intercalation in the 7H pyrido[4,3-c] carbazole family: a comparative 1H and 31P NMR study** - M.DELEPIERRE, R.MAROUN, C.MILLET, C.GARBAY, J.IGOLEN°, B.ROQUES - Chimie organique, UA CNRS 498, Paris 75006 et °Chimie organique, Institut Pasteur

51 B - **Modelization of the disulfide bridge in proteins: ab initio-CI studies of S_2H_2 and $S_2(CH_3)_2$** - M.LOOS, Chimie théorique, Nancy I

WITHDRAWALS

Molecular surface calculations in biomolecules, molecular area-solubility relationship - E.SILLA, Valencia, Spain

Modelling transition structures in enzyme-active sites - E.SILLA, Valencia

CHANGES IN TITLES

28 is now: **The Na^+ ion solvation in water-HMPT solution: MD simulation**

28 C is now: **Kinetic modelling of heterogeneous-catalyzed reactions with the ANACIN software. Application to the hydrodenitrogenation of phenanthridine**

30 is now: **NMR studies of proteins and protein-DNA interactions**
Family reasons prevent Prof. Boelens from attending. The lecture will be presented by his coworker Dr J.A.C.RULLMANN

55 is now: **Electrostatic Basis for Protein Functions: Incorporating the Environment in Microscopic Calculations of Free-Energy and Dynamics of Chemical Processes in Solutions and Proteins**

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MODELISATION MOLECULAIRE EN CHIMIE PHYSIQUE

Université de NANCY I
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